Royal College *of* OBSTETRICIANS *and* GYNAECOLOGISTS

The Royal College of Midwives

Hypertension in pregnancy: the management of hypertensive disorders during pregnancy

August 2010 (revised reprint January 2011)

NICE Clinical Guideline

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Hypertension in pregnancy

the management of hypertensive disorders during pregnancy

National Collaborating Centre for Women's and Children's Health

Commissioned by the National Institute for Health and Clinical Excellence

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This guideline has been developed by the National Collaborating Centre for Women's and Children's Health, which is an intercollegiate collaboration between the Royal College of Obstetricians and Gynaecologists, the Royal College of Paediatrics and Child Health and the Royal College of Midwives. The principal aim of the work undertaken by the National Collaborating Centre for Women's and Children's Health and its partners is to improve outcomes and choice for women, children and their families by producing national clinical guidelines that promote high-quality cost-effective care within the NHS.

This guideline has been fully funded by NICE. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient.

Implementation of this guidance is the responsibility of local commissioners and/or providers.

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Appendices E–G are in separate files.

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1 Summary of recommendations and care pathway

This clinical guideline contains recommendations for the diagnosis and management of hypertensive disorders during pregnancy in the antenatal, intrapartum and postnatal periods. It includes recommendations for women with chronic hypertension who wish to conceive and recommendations for advice to women after a pregnancy complicated by hypertension.

This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

This guideline recommends some drugs for indications for which they do not have a UK marketing authorisation at the date of publication, if there is good evidence to support that use. Many drugs do not have a licence for use specifically in pregnant women, reflecting the fact that this group is often excluded from studies. Unlicensed drugs are marked with an asterisk.

1.1 Key priorities for implementation

Reducing the risk of hypertensive disorders in pregnancy

Advise women at high risk of pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

Management of pregnancy with chronic hypertension

Tell women who take angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs):

- that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy
- to discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

In pregnant women with chronic hypertension aim to keep blood pressure lower than 150/100 mmHg.

Assessment of proteinuria in hypertensive disorders of pregnancy

Use an automated reagent-strip reading device or a spot urinary protein:creatinine ratio for estimating proteinuria in a secondary care setting.

* In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

Management of pregnancy with gestational hypertension

Offer women with gestational hypertension an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in the table below.

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	No	No	Yes (until blood pressure is 159/109 mmHg or lower)
Treat	No	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg
Measure blood pressure	Not more than once a week	At least twice a week	At least four times a day
Test for proteinuria	At each visit using automated reagent-strip reading device or urinary protein : creatinine ratio	At each visit using automated reagent-strip reading device or urinary protein : creatinine ratio	Daily using automated reagent-strip reading device or urinary protein : creatinine ratio
Blood tests	Only those for routine antenatal care	Test kidney function, electrolytes, full blood count, transaminases, bilirubin Do not carry out further blood tests if no proteinuria at subsequent visits	Test at presentation and then monitor weekly: • kidney function, electrolytes, full blood count, transaminases, bilirubin

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Management of pregnancy with pre-eclampsia

Offer women with pre-eclampsia an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in the table below.

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg
Measure blood pressure	At least four times a day	At least four times a day	More than four times a day, depending on clinical circumstances
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor using the following tests twice a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin

Consultant obstetric staff should document in the woman's notes the maternal (biochemical, haematological and clinical) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia.

Offer all women who have had pre-eclampsia a medical review at the postnatal review (6–8 weeks after the birth).

Advice and follow-up care at transfer to community care

Tell women who had pre-eclampsia that their risk of developing:

- gestational hypertension in a future pregnancy ranges from about 1 in 8 (13%) pregnancies to about 1 in 2 (53%) pregnancies
- pre-eclampsia in a future pregnancy is up to about 1 in 6 (16%) pregnancies
- pre-eclampsia in a future pregnancy is about 1 in 4 (25%) pregnancies if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and about 1 in 2 (55%) pregnancies if it led to birth before 28 weeks.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

1.2 Recommendations

Definitions

For the purposes of this guideline, the following definitions apply.

- Chronic hypertension is hypertension that is present at the booking visit or before 20 weeks or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology.
- Eclampsia is a convulsive condition associated with pre-eclampsia.
- HELLP syndrome is haemolysis, elevated liver enzymes and low platelet count.
- Gestational hypertension is new hypertension presenting after 20 weeks without significant proteinuria.
- Pre-eclampsia is new hypertension presenting after 20 weeks with significant proteinuria.
- Severe pre-eclampsia is pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment.
- Significant proteinuria is if there is more than 300 mg protein in a 24-hour urine collection or more than 30 mg/mmol in a spot urinary protein : creatinine sample.

In addition, the Guideline Development Group (GDG) has defined mild, moderate and severe hypertension to help with implementation of this guidance as follows:

- Mild hypertension: diastolic blood pressure 90–99 mmHg, systolic blood pressure 140–149 mmHg.
- Moderate hypertension: diastolic blood pressure 100–109 mmHg, systolic blood pressure 150–159 mmHg.
- Severe hypertension: diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater.

Techniques for the measurement of blood pressure in pregnancy are described in 'Antenatal care' (NICE clinical guideline 62).

In this guideline 'offer birth' means to offer elective early birth through induction of labour or by elective caesarean section if indicated.

Chapter 3 Reducing the risk of hypertensive disorders in pregnancy

Symptoms of pre-eclampsia

Pregnant women should be made aware of the need to seek immediate advice from a healthcare professional if they experience symptoms of pre-eclampsia. Symptoms include:

- severe headache
- problems with vision, such as blurring or flashing before the eyes
- severe pain just below the ribs
- vomiting
- sudden swelling of the face, hands or feet.

[This recommendation is adapted from 'Antenatal care' (NICE clinical guideline 62).]

Antiplatelet agents

Advise women at high risk of pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

* In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

Advise women with more than one moderate risk factor for pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Factors indicating moderate risk are:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- body mass index (BMI) of 35 kg/m² or more at first visit
- family history of pre-eclampsia
- multiple pregnancy.

Other pharmaceutical agents

Do not use the following to prevent hypertensive disorders during pregnancy:

- nitric oxide donors
- progesterone
- diuretics
- low molecular weight heparin.

Nutritional supplements

Do not recommend the following supplements solely with the aim of preventing hypertensive disorders during pregnancy:

- magnesium
- folic acid
- antioxidants (vitamins C and E)
- fish oils or algal oils
- garlic.

Diet

Do not recommend salt restriction during pregnancy solely to prevent gestational hypertension or pre-eclampsia.

Lifestyle

Advice on rest, exercise and work for women at risk of hypertensive disorders during pregnancy should be the same as for healthy pregnant women (see 'Antenatal care', NICE clinical guideline 62).

Chapter 4 Management of pregnancy with chronic hypertension

Women with chronic hypertension should be given advice and treatment in line with 'Hypertension: the management of hypertension in adults in primary care' (NICE clinical guideline 34), unless it specifically differs from recommendations in this guideline.

Pre-pregnancy advice

Tell women who take angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs):

- that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy
- to discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

Stop antihypertensive treatment in women taking ACE inhibitors or ARBs if they become pregnant (preferably within 2 working days of notification of pregnancy) and offer alternatives.

* In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

Tell women who take chlorothiazide:

- that there may be an increased risk of congenital abnormality and neonatal complications if these drugs are taken during pregnancy
- to discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

Tell women who take antihypertensive treatments other than ACE inhibitors, ARBs or chlorothiazide that the limited evidence available has not shown an increased risk of congenital malformation with such treatments.

Diet

Encourage women with chronic hypertension to keep their dietary sodium intake low, either by reducing or substituting sodium salt, because this can reduce blood pressure. [This recommendation is adapted from 'Hypertension: management of hypertension in adults in primary care' (NICE clinical guideline 34).]

Treatment of hypertension

In pregnant women with uncomplicated chronic hypertension aim to keep blood pressure less than 150/100 mmHg.

Do not offer pregnant women with uncomplicated chronic hypertension treatment to lower diastolic blood pressure below 80 mmHg.

Offer pregnant women with target-organ damage secondary to chronic hypertension (for example, kidney disease) treatment with the aim of keeping blood pressure lower than 140/90 mmHg.

Offer pregnant women with secondary chronic hypertension referral to a specialist in hypertensive disorders.

Offer women with chronic hypertension antihypertensive treatment dependent on pre-existing treatment, side-effect profiles and teratogenicity.

Antenatal consultations

In women with chronic hypertension, schedule additional antenatal consultations based on the individual needs of the woman and her baby.

Timing of birth

Do not offer birth to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment before 37 weeks.

For women with chronic hypertension whose blood pressure is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician.

Offer birth to women with refractory severe chronic hypertension, after a course of corticosteroids (if required) has been completed.

Postnatal investigation, monitoring and treatment

In women with chronic hypertension who have given birth, measure blood pressure:

- daily for the first two days after birth
- at least once between day 3 and day 5 after birth
- as clinically indicated if antihypertensive treatment is changed after birth.

In women with chronic hypertension who have given birth, aim to keep blood pressure lower than 140/90 mmHg.

In women with chronic hypertension who have given birth:

- continue antenatal antihypertensive treatment.
- review long-term antihypertensive treatment 2 weeks after the birth.

If a woman has taken methyldopa† to treat chronic hypertension during pregnancy, stop within 2 days of birth and restart the antihypertensive treatment the woman was taking before she planned the pregnancy.

Offer women with chronic hypertension a medical review at the postnatal review (6–8 weeks after the birth) with the pre-pregnancy care team.

Chapter 5 Assessment of proteinuria in hypertensive disorders of pregnancy

Use an automated reagent-strip reading device or a spot urinary protein:creatinine ratio for estimating proteinuria in a secondary care setting.

If an automated reagent-strip reading device is used to detect proteinuria and a result of 1+ or more is obtained, use a spot urinary protein:creatinine ratio or 24-hour urine collection to quantify proteinuria.

Diagnose significant proteinuria if the urinary protein:creatinine ratio is greater than 30 mg/mmol or a validated 24-hour urine collection result shows greater than 300 mg protein.

Where 24-hour urine collection is used to quantify proteinuria, there should be a recognised method of evaluating completeness of the sample.

Chapter 6 Management of pregnancy with gestational hypertension

Treatment of hypertension

In women with gestational hypertension full assessment should be carried out in a secondary care setting by a healthcare professional who is trained in the management of hypertensive disorders.

In women with gestational hypertension, take account of the following risk factors that require additional assessment and follow-up:

- nulliparity
- age 40 years or older
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- multiple pregnancy
- BMI of 35 kg/m² or more
- gestational age at presentation
- previous history of pre-eclampsia or gestational hypertension
- pre-existing vascular disease
- pre-existing kidney disease.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Offer women with gestational hypertension an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in the table below.

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	No	No	Yes (until blood pressure is 159/109 mmHg or lower)
Treat	No	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg
Measure blood pressure	Not more than once a week	At least twice a week	At least four times a day
Test for proteinuria	At each visit using automated reagent-strip reading device or urinary protein : creatinine ratio	At each visit using automated reagent-strip reading device or urinary protein : creatinine ratio	Daily using automated reagent-strip reading device or urinary protein : creatinine ratio
Blood tests	Only those for routine antenatal care	Test kidney function, electrolytes, full blood count, transaminases, bilirubin Do not carry out further blood tests if no proteinuria at subsequent visits	Test at presentation and then monitor weekly: • kidney function, electrolytes, full blood count, transaminases, bilirubin

Only offer women with gestational hypertension antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine.†

In women receiving outpatient care for severe gestational hypertension, after it has been effectively controlled in hospital, measure blood pressure and test urine twice weekly and carry out weekly blood tests.

In women with mild hypertension presenting before 32 weeks, or at high risk of pre-eclampsia, measure blood pressure and test urine twice weekly.

Do not offer bed rest in hospital as a treatment for gestational hypertension.

Timing of birth

Do not offer birth before 37 weeks to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment.

For women with gestational hypertension whose blood pressure is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician.

Offer birth to women with refractory severe gestational hypertension after a course of corticosteroids (if required) has been completed.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Postnatal investigation, monitoring and treatment

In women with gestational hypertension who have given birth, measure blood pressure:

- daily for the first 2 days after birth
- at least once between day 3 and day 5 after birth
- as clinically indicated if antihypertensive treatment is changed after birth.

In women with gestational hypertension who have given birth:

- continue use of antenatal antihypertensive treatment
- consider reducing antihypertensive treatment if their blood pressure falls below 140/90 mmHg
- reduce antihypertensive treatment if their blood pressure falls below 130/80 mmHg.

If a woman has taken methyldopa† to treat gestational hypertension, stop within 2 days of birth.

For women with gestational hypertension who did not take antihypertensive treatment and have given birth, start antihypertensive treatment if their blood pressure is higher than 149/99 mmHg.

Write a care plan for women with gestational hypertension who have given birth and are being transferred to community care that includes all of the following:

- who will provide follow-up care, including medical review if needed
- frequency of blood pressure monitoring needed
- thresholds for reducing or stopping treatment
- indications for referral to primary care for blood pressure review.

Offer women who have had gestational hypertension and remain on antihypertensive treatment 2 weeks after transfer to community care, a medical review.

Offer women who have had gestational hypertension a medical review at the postnatal review (6–8 weeks after the birth).

Offer women who have had gestational hypertension and who still need antihypertensive treatment at the postnatal review (6–8 weeks after the birth) a specialist assessment of their hypertension.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Chapter 7 Management of pregnancy with pre-eclampsia

Treatment of hypertension

Assess women with pre-eclampsia at each consultation. Assessment should be performed by a healthcare professional trained in the management of hypertensive disorders of pregnancy.

Offer women with pre-eclampsia an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in the table below.

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg
Measure blood pressure	At least four times a day	At least four times a day	More than four times a day, depending on clinical circumstances
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor using the following tests twice a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin

Only offer women with pre-eclampsia antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine.†

Timing of birth

Manage pregnancy in women with pre-eclampsia conservatively (that is, do not plan same-day delivery of the baby) until 34 weeks.

Consultant obstetric staff should document in the woman's notes the maternal (biochemical, haematological and clinical) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia.

Consultant obstetric staff should write a plan for antenatal fetal monitoring during birth.

Offer birth to women with pre-eclampsia before 34 weeks, after discussion with neonatal and anaesthetic teams and a course of corticosteroids has been given if:

- severe hypertension develops refractory to treatment
- maternal or fetal indications develop as specified in the consultant plan.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Recommend birth for women who have pre-eclampsia with severe hypertension after 34 weeks when their blood pressure has been controlled and a course of corticosteroids has been completed (if appropriate).

Offer birth to women who have pre-eclampsia with mild or moderate hypertension at 34^{+0} to 36^{+6} weeks depending on maternal and fetal condition, risk factors and availability of neonatal intensive care.

Recommend birth within 24–48 hours for women who have pre-eclampsia with mild or moderate hypertension after 37^{+0} weeks.

Postnatal investigation, monitoring and treatment (including after discharge from critical care)

Blood pressure

In women with pre-eclampsia who did not take antihypertensive treatment and have given birth, measure blood pressure:

- at least four times a day while the woman is an inpatient
- at least once between day 3 and day 5 after birth
- on alternate days until normal if blood pressure was abnormal on days 3–5.

In women with pre-eclampsia who did not take antihypertensive treatment and have given birth, start antihypertensive treatment if blood pressure is 150/100 mmHg or higher

Ask women with pre-eclampsia who have given birth about severe headache and epigastric pain each time blood pressure is measured.

In women with pre-eclampsia who took antihypertensive treatment and have given birth, measure blood pressure:

- at least four times a day while the woman is an inpatient
- every 1–2 days for up to 2 weeks after transfer to community care until the woman is off treatment and has no hypertension.

For women with pre-eclampsia who have taken antihypertensive treatment and have given birth:

- continue antenatal antihypertensive treatment
- consider reducing antihypertensive treatment if their blood pressure falls below 140/90 mmHg
- reduce antihypertensive treatment if their blood pressure falls below 130/80 mmHg.

If a woman has taken methyldopa[†] to treat pre-eclampsia, stop within 2 days of birth.

Offer women with pre-eclampsia who have given birth transfer to community care if all of the following criteria have been met:

- there are no symptoms of pre-eclampsia
- blood pressure, with or without treatment, is 149/99 mmHg or lower
- blood test results are stable or improving.

Write a care plan for women with pre-eclampsia who have given birth and are being transferred to community care that includes all of the following:

- who will provide follow-up care, including medical review if needed
- frequency of blood pressure monitoring
- thresholds for reducing or stopping treatment
- indications for referral to primary care for blood pressure review
- self-monitoring for symptoms

Offer women who have pre-eclampsia and are still on antihypertensive treatment 2 weeks after transfer to community care a medical review.

[†] This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Offer all women who have had pre-eclampsia a medical review at the postnatal review (6–8 weeks after the birth).

Offer women who have had pre-eclampsia and who still need antihypertensive treatment at the postnatal review (6–8 weeks after the birth) a specialist assessment of their hypertension.

Haematological and biochemical monitoring

In women who have pre-eclampsia with mild or moderate hypertension or after step-down from critical care:

- measure platelet count, transaminases and serum creatinine 48–72 hours after birth or step-down
- do not repeat platelet count, transaminases or serum creatinine measurements if results are normal at 48–72 hours.

If biochemical and haematological indices are improving but stay within the abnormal range in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated and at the postnatal review (6–8 weeks after the birth).

If biochemical and haematological indices are not improving relative to pregnancy ranges in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated.

In women with pre-eclampsia who have given birth, carry out a urinary reagent-strip test at the postnatal review (6–8 weeks after the birth).

In women with pre-eclampsia who have given birth and have stepped down from critical care level 2, do not measure fluid balance if creatinine is within the normal range.

Offer women who had pre-eclampsia and still have proteinuria (1+ or more) at the postnatal review (6–8 weeks after the birth) a further review at 3 months after the birth to assess kidney function and consider offering them a referral for specialist kidney assessment.

Chapter 8 Fetal monitoring

Chronic hypertension

In women with chronic hypertension, carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry between 28 and 30 weeks and between 32 and 34 weeks. If results are normal, do not repeat at more than 34 weeks, unless otherwise clinically indicated.

In women with chronic hypertension, only carry out cardiotocography if fetal activity is abnormal.

Mild or moderate gestational hypertension

In women with mild or moderate gestational hypertension, carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry if diagnosis is confirmed at less than 34 weeks. If results are normal, do not repeat at more than 34 weeks, unless otherwise clinically indicated.

In women with mild or moderate gestational hypertension, do not carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry if diagnosis is confirmed after 34 weeks, unless otherwise clinically indicated.

In women with mild or moderate gestational hypertension, only carry out cardiotocography if fetal activity is abnormal.

Severe gestational hypertension or pre-eclampsia

Carry out cardiotocography at diagnosis of severe gestational hypertension or pre-eclampsia.

If conservative management of severe gestational hypertension or pre-eclampsia is planned carry out all the following tests at diagnosis:

- ultrasound fetal growth and amniotic fluid volume assessment.
- umbilical artery Doppler velocimetry.

If the results of all fetal monitoring are normal in women with severe gestational hypertension or pre-eclampsia, do not routinely repeat cardiotocography more than weekly.

In women with severe gestational hypertension or pre-eclampsia, repeat cardiotocography if any of the following occur:

- the woman reports a change in fetal movement
- vaginal bleeding
- abdominal pain
- deterioration in maternal condition.

In women with severe gestational hypertension or pre-eclampsia, do not routinely repeat ultrasound fetal growth and amniotic fluid volume assessment or umbilical artery Doppler velocimetry more than every 2 weeks.

If the results of any fetal monitoring in women with severe gestational hypertension or pre-eclampsia are abnormal, tell a consultant obstetrician.

For women with severe gestational hypertension or pre-eclampsia, write a care plan that includes all of the following:

- the timing and nature of future fetal monitoring
- fetal indications for birth and if and when corticosteroids should be given
- when discussion with neonatal paediatricians and obstetric anaesthetists should take place and what decisions should be made.

Women at high risk of pre-eclampsia

Carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry starting at between 28 and 30 weeks (or at least 2 weeks before previous gestational age of onset if earlier than 28 weeks) and repeating 4 weeks later in women with previous:

- severe pre-eclampsia
- pre-eclampsia that needed birth before 34 weeks
- pre-eclampsia with a baby whose birth weight was less than the 10th centile
- intrauterine death
- placental abruption.

In women who are at high risk of pre-eclampsia only carry out cardiotocography if fetal activity is abnormal.

Chapter 9 Intrapartum care

Women with hypertensive disorders during pregnancy should be given advice and treatment in line with 'Intrapartum care: management and delivery of care to women in labour' (NICE clinical guideline 55), unless it specifically differs from recommendations in this guideline.

Blood pressure

During labour, measure blood pressure:

- hourly in women with mild or moderate hypertension
- continually in women with severe hypertension.

Continue use of antenatal antihypertensive treatment during labour.

Haematological and biochemical monitoring

Determine the need for haematological and biochemical tests during labour in women with mild or moderate hypertension using the same criteria as in the antenatal period even if regional analgesia is being considered.

Care during epidural analgesia

Do not preload women who have severe pre-eclampsia with intravenous fluids before establishing low-dose epidural analgesia and combined spinal epidural analgesia.

Management of the second stage of labour

Do not routinely limit the duration of the second stage of labour:

- in women with stable mild or moderate hypertension or
- if blood pressure is controlled within target ranges in women with severe hypertension.

Recommend operative birth in the second stage of labour for women with severe hypertension whose hypertension has not responded to initial treatment.

Chapter 10 Medical management of severe hypertension or severe pre-eclampsia in a critical care setting

Anticonvulsants

If a woman in a critical care setting who has severe hypertension or severe pre-eclampsia has or previously had an eclamptic fit, give intravenous magnesium sulphate.*

Consider giving intravenous magnesium sulphate* to women with severe pre-eclampsia who are in a critical care setting if birth is planned within 24 hours.

If considering magnesium sulphate* treatment, use the following as features of severe pre-eclampsia:

- severe hypertension and proteinuria **or**
- mild or moderate hypertension and proteinuria with one or more of the following:
  - symptoms of severe headache
  - problems with vision, such as blurring or flashing before the eyes
  - severe pain just below the ribs or vomiting
  - papilloedema
  - signs of clonus (≥ 3 beats)
  - liver tenderness
  - HELLP syndrome
  - platelet count falling to below 100×10^9 per litre
  - abnormal liver enzymes (ALT or AST rising to above 70 IU/litre).

Use the Collaborative Eclampsia Trial§ regimen for administration of magnesium sulphate:*

- loading dose of 4 g should be given intravenously over 5 minutes, followed by an infusion of 1 g/hour maintained for 24 hours
- recurrent seizures should be treated with a further dose of 2–4 g given over 5 minutes.

Do not use diazepam, phenytoin or lytic cocktail as an alternative to magnesium sulphate* in women with eclampsia.

* In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

§ The Eclampsia Trial Collaborative Group (1995) Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 345:1455–63.

Antihypertensives

Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with one of the following:

- labetalol[†] (oral or intravenous)
- hydralazine (intravenous)
- nifedipine[†] (oral).

In women with severe hypertension who are in critical care, monitor their response to treatment:

- to ensure that their blood pressure falls
- to identify adverse effects for both the woman and the fetus
- to modify treatment according to response.

Consider using up to 500 ml crystalloid fluid before or at the same time as the first dose of intravenous hydralazine in the antenatal period.

In women with severe hypertension who are in critical care, aim to keep systolic blood pressure below 150 mmHg and diastolic blood pressure between 80 and 100 mmHg.

Corticosteroids for fetal lung maturation

If birth is considered likely within 7 days in women with pre-eclampsia:

- give two doses of betamethasone[*] 12 mg intramuscularly 24 hours apart in women between 24 and 34 weeks
- consider giving two doses of betamethasone[*] 12 mg intramuscularly 24 hours apart in women between 35 and 36 weeks.

Corticosteroids to manage HELLP syndrome

Do not use dexamethasone or betamethasone for the treatment of HELLP syndrome.

Fluid balance and volume expansion

Do not use volume expansion in women with severe pre-eclampsia unless hydralazine is the antenatal antihypertensive.

In women with severe pre-eclampsia, limit maintenance fluids to 80 ml/hour unless there are other ongoing fluid losses (for example, haemorrhage).

Caesarean section versus induction of labour

Choose mode of birth for women with severe hypertension, severe pre-eclampsia or eclampsia according to the clinical circumstances and the woman's preference.

[†] This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

[*] In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

Indications for referral to critical care levels

Offer women with severe hypertension or severe pre-eclampsia referral to the appropriate critical care setting using the following criteria:[‡]

Level 3 care	• Severe pre-eclampsia and needing ventilation
Level 2 care	Step-down from level 3 or severe pre-eclampsia with any of the following complications: • eclampsia • HELLP syndrome • haemorrhage • hyperkalaemia • severe oliguria • coagulation support • intravenous antihypertensive treatment • initial stabilisation of severe hypertension • evidence of cardiac failure • abnormal neurology
Level 1 care	• Pre-eclampsia with mild or moderate hypertension • Ongoing conservative antenatal management of severe preterm hypertension • Step-down treatment after the birth

Chapter 11 Breastfeeding

In women who still need antihypertensive treatment in the postnatal period, avoid diuretic treatment for hypertension if the woman is breastfeeding or expressing milk.

Tell women who still need antihypertensive treatment in the postnatal period that the following antihypertensive drugs have no known adverse effects on babies receiving breast milk:

- labetalol[†]
- nifedipine[†]
- enalapril[†]
- captopril[†]
- atenolol[†]
- metoprolol.[†]

Tell women who still need antihypertensive treatment in the postnatal period that there is insufficient evidence on the safety in babies receiving breast milk of the following antihypertensive drugs:

- ARBs
- amlodipine
- ACE inhibitors other than enalapril[†] and captopril.[†]

Assess the clinical wellbeing of the baby, especially adequacy of feeding, at least daily for the first 2 days after the birth.

[‡] Adapted from Intensive Care Society, Standards and Guidelines 2002.

[†] This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Chapter 12 Advice and follow-up care at transfer to community care

Long-term risk of cardiovascular disease

Tell women who have had gestational hypertension or pre-eclampsia, and their primary care clinicians, that these conditions are associated with an increased risk of developing high blood pressure and its complications in later life.

Long-term risk of end-stage kidney disease

Tell women with a history of pre-eclampsia who have no proteinuria and no hypertension at the postnatal review (6–8 weeks after the birth) that although the relative risk of kidney disease is increased the absolute risk is low and no further follow-up is necessary.

Thrombophilia and the risk of pre-eclampsia

Do not routinely perform screening for thrombophilia in women who have had pre-eclampsia.

Risk of recurrence of hypertensive disorders of pregnancy

Tell women who had gestational hypertension that their risk of developing:

- gestational hypertension in a future pregnancy ranges from about 1 in 6 (16%) pregnancies to about 1 in 2 (47%) pregnancies
- pre-eclampsia in a future pregnancy ranges from 1 in 50 (2%) to about 1 in 14 (7%) pregnancies.

Tell women who had pre-eclampsia that their risk of developing:

- gestational hypertension in a future pregnancy ranges from about 1 in 8 (13%) pregnancies to about 1 in 2 (53%) pregnancies
- pre-eclampsia in a future pregnancy is up to about 1 in 6 (16%) pregnancies
- pre-eclampsia in a future pregnancy is about 1 in 4 (25%) pregnancies if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and about 1 in 2 (55%) pregnancies if it led to birth before 28 weeks.

Interpregnancy interval and recurrence of hypertensive disorders of pregnancy

Tell women who have had pre-eclampsia that there is no additional risk of recurrence with interpregnancy interval up to 10 years.

Body mass index and recurrence of hypertensive disorders of pregnancy

Advise women who have had pre-eclampsia to achieve and keep a BMI within the healthy range before their next pregnancy (18.5–24.9 kg/m², 'Obesity', NICE clinical guideline 43).

1.3 Key priorities for research

Reducing the risk of hypertensive disorders in pregnancy

How clinically and cost effective is calcium supplementation (compared with placebo) for the prevention of pre-eclampsia in women at both moderate and high risk of pre-eclampsia?

Why this is important

Pre-eclampsia and gestational hypertension represent common pregnancy complications. Although large studies on the use of calcium supplementation to prevent hypertensive disorders during pregnancy have been carried out, the variation in populations and calcium status at entry to the studies has made it impossible to reach a conclusion on the value of such treatment in any setting. Calcium supplementation as a treatment is cheap, likely to be well tolerated, and likely to be safe for both the woman and the fetus, although this needs to be confirmed. Even a modest effect would be potentially important given the simplicity of the treatment. A new meta-analysis, using the technique of meta-analysis regression, is needed to clarify the roles of dietary calcium intake and underlying pre-eclampsia risk, taking advantage of subgroup data and

seeking additional information from the authors of published trials where possible. Further randomised controlled trials could also be conducted to examine risk reduction in women at moderate and high risk of pre-eclampsia, and to re-examine risk reduction in women at low risk of pre-eclampsia. These trials should consider maternal diet and calcium status and they should evaluate both maternal outcomes (incidence of hypertensive diseases during pregnancy, including severe disease) and neonatal or infant outcomes (neonatal morbidity, infant growth and development).

Assessment of proteinuria in hypertensive disorders of pregnancy

How should significant proteinuria be defined in women with hypertension during pregnancy?

Why this is important

Most adverse outcomes in new-onset hypertensive disorders during pregnancy arise in women with proteinuria. However, the quality of evidence for the diagnosis of significant proteinuria is poor and the prognostic value of different quantities of urinary protein is unclear. There is a need for large, high-quality prospective studies comparing the various methods of measuring proteinuria (automated reagent-strip reading devices, urinary protein : creatinine ratio, urinary albumin : creatinine ratio, and 24-hour urine collection) in women with new-onset hypertensive disorders during pregnancy. The studies should aim to determine which method of measurement, and which diagnostic thresholds, are most accurate in predicting clinically important outcomes. Such studies would inform decisions regarding clinical management of new-onset hypertensive disorders during pregnancy. If predictive parameters were identified then interventions based on these and aimed at improving outcomes could be evaluated in randomised clinical trials.

Haematological and biochemical monitoring in women with gestational hypertension

What is the role of assessing haematological or biochemical parameters at diagnosis of gestational hypertension and during surveillance of gestational hypertension?

Why this is important

Pre-eclampsia is a multisystem disorder, but it is not clear whether routine assessment of a range of haematological or biochemical parameters in women with gestational hypertension helps clinical care or is sufficiently discriminatory to allow better targeted care. Information on which assessments might be useful is incomplete and there are confusing data on whether clinical outcomes are changed.

Large prospective studies should be carried out to examine a range of parameters singly and serially (kidney function, liver function, coagulation, measurement of proteinuria) in women with gestational hypertension. These studies should use properly validated pregnancy values and examine the prediction of clinically important outcomes (severe pre-eclampsia and its maternal and fetal complications).

If parameters with sufficient prediction are identified, randomised controlled trials should be used to compare the effect of knowledge of these compared with no knowledge on clinical maternal and perinatal outcomes. Trial results should be incorporated in health economic models to assess cost effectiveness.

Timing of birth in women with pre-eclampsia

When should women who have pre-eclampsia with mild or moderate hypertension give birth?

Why this is important

There is a 'grey' zone for women who have pre-eclampsia with mild or moderate hypertension between 34 and 37 weeks when the optimal timing of birth is not clear.

Women who have pre-eclampsia with mild or moderate hypertension may progress to severe disease with its risks, but it is not clear whether these risks outweigh or should outweigh the risks of planned late preterm birth for the baby. Neonatal services are under constant pressure and planned preterm birth without clear benefit to either woman or baby would have costs.

Randomised controlled trials should be carried out that compare policies of immediate planned birth between 34^{+0} and 36^{+6} weeks in women who have pre-eclampsia with mild or moderate hypertension with expectant management and birth for clinical progression. Outcomes should include severe pre-eclampsia and its complications, need for critical care, maternal satisfaction, neonatal morbidity and mortality, and health economics. Trials need to be large enough to examine less common complications in the woman.

Antihypertensive agents and breastfeeding

How safe are commonly used antihypertensive agents when used by women who are breastfeeding?

Why this is important

With the increasing incidence of hypertensive disorders during pregnancy, more pregnant and breastfeeding women will potentially be exposed to antihypertensive medication. Most of the relevant drugs are not licensed for use in pregnancy. For most drugs there is no information on their presence in human breast milk, or if such a presence has any clinical effect. As a result, women may either be denied effective treatment in the postnatal period or advised against breastfeeding. Studies should measure the concentration of relevant drugs and their metabolites in breast milk, taking account of drug pharmacokinetics (peak levels and elimination) and comparing neonatal behaviour and physiological variables in women using each drug with those in women who choose not to breastfeed. Studies should follow women and their babies for long enough to exclude cumulative effects and they should be large enough to provide reassurance to licensing and drug regulating authorities.

1.4 Research recommendations

Reducing the risk of hypertensive disorders in pregnancy

What is the clinical and cost effectiveness of aspirin prophylaxis for the prevention of pre-eclampsia in women with at least two moderate risk factors?

Why this is important

Although the evidence for the use of low-dose aspirin to reduce the risk of pre-eclampsia in women at high risk is clear, the benefits for those at moderate risk are more difficult to establish and research is required for this group. A problem with the available evidence is the difficulty in quantifying benefit for individual moderate risk factors and determining what interactions exist between them. Although low-dose aspirin appears a safe drug to use in pregnancy there needs to be clearer evidence of benefit within the moderate-risk group of women.

How clinically and cost effective is calcium supplementation (compared with placebo) for the prevention of pre-eclampsia in women at both moderate and high risk of pre-eclampsia?

Why this is important

Pre-eclampsia and gestational hypertension represent common pregnancy complications. Although large studies on the use of calcium supplementation to prevent hypertensive disorders during pregnancy have been carried out, the variation in populations and calcium status at entry to the studies has made it impossible to reach a conclusion on the value of such treatment in any setting. Calcium supplementation as a treatment is cheap, likely to be well tolerated, and likely to be safe for both the woman and the fetus, although this needs to be confirmed. Even a modest effect would be potentially important given the simplicity of the treatment. A new meta-analysis, using the technique of meta-analysis regression, is needed to clarify the roles of dietary calcium intake and underlying pre-eclampsia risk, taking advantage of subgroup data and seeking additional information from the authors of published trials where possible. Further randomised controlled trials could also be conducted to examine risk reduction in women at moderate and high risk of pre-eclampsia, and to re-examine risk reduction in women at low risk of pre-eclampsia. These trials should consider maternal diet and calcium status and they should evaluate both maternal outcomes (incidence of hypertensive diseases during pregnancy, including severe disease) and neonatal or infant outcomes (neonatal morbidity, infant growth and development).

Management of pregnancy with chronic hypertension

Which antihypertensive agent is best for use in women with chronic hypertension during pregnancy?

Why this is important

The literature on anti-hypertensive medication in women with chronic hypertension is inadequate to determine if any particular agent would offer advantages over placebo control or other antihypertensive agents. All drugs in common use have potential side effects and potential fetal and neonatal effects. As chronic hypertension is becoming more common it seems sensible to revisit therapy to ensure both efficacy and safety. Randomised controlled trials should be carried out in women with chronic hypertension during pregnancy to assess the commonly used antihypertensive agents relative to placebo control, and to compare different antihypertensives using head-to-head trials. Outcomes of interest are: level of blood pressure control for each type of drug, incidence of pre-eclampsia and complications of severe hypertension, efficacy, side effects, and perinatal morbidity and mortality.

Assessment of proteinuria in hypertensive disorders of pregnancy

How should significant proteinuria be defined in women with hypertension during pregnancy?

Why this is important

Most adverse outcomes in new-onset hypertensive disorders during pregnancy arise in women with proteinuria. However, the quality of evidence for the diagnosis of significant proteinuria is poor and the prognostic value of different quantities of urinary protein is unclear. There is a need for large, high-quality prospective studies comparing the various methods of measuring proteinuria (automated reagent-strip reading devices, urinary protein:creatinine ratio, urinary albumin:creatinine ratio, and 24-hour urine collection) in women with new-onset hypertensive disorders during pregnancy. The studies should aim to determine which method of measurement, and which diagnostic thresholds, are most accurate in predicting clinically important outcomes. Such studies would inform decisions regarding clinical management of new-onset hypertensive disorders during pregnancy. If predictive parameters were identified then interventions based on these and aimed at improving outcomes could be evaluated in randomised clinical trials.

Haematological and biochemical monitoring in women with gestational hypertension

What is the role of assessing haematological or biochemical parameters at diagnosis of gestational hypertension and during surveillance of gestational hypertension?

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Pre-eclampsia is a multisystem disorder, but it is not clear whether routine assessment of a range of haematological or biochemical parameters in women with gestational hypertension helps clinical care or is sufficiently discriminatory to allow better targeted care. Information on which assessments might be useful is incomplete and there are confusing data on whether clinical outcomes are changed.

Large prospective studies should be carried out to examine a range of parameters singly and serially (kidney function, liver function, coagulation, measurement of proteinuria) in women with gestational hypertension. These studies should use properly validated pregnancy values and examine the prediction of clinically important outcomes (severe pre-eclampsia and its maternal and fetal complications).

If parameters with sufficient prediction are identified, randomised controlled trials should be used to compare the effect of knowledge of these compared with no knowledge on clinical maternal and perinatal outcomes. Trial results should be incorporated in health economic models to assess cost effectiveness.

Timing of birth in women with pre-eclampsia

When should women who have pre-eclampsia with mild or moderate hypertension give birth?

Why this is important

There is a 'grey' zone for women who have pre-eclampsia with mild or moderate hypertension between 34 and 37 weeks when the optimal timing of birth is not clear.

Women who have pre-eclampsia with mild or moderate hypertension may progress to severe disease with its risks, but it is not clear whether these risks outweigh or should outweigh the risks of planned late preterm birth for the baby. Neonatal services are under constant pressure and planned preterm birth without clear benefit to either woman or baby would have costs.

Randomised controlled trials should be carried out that compare policies of immediate planned birth between 34^{+0} and 36^{+6} weeks in women who have pre-eclampsia with mild or moderate hypertension with expectant management and birth for clinical progression. Outcomes should include severe pre-eclampsia and its complications, need for critical care, maternal satisfaction, neonatal morbidity and mortality, and health economics. Trials need to be large enough to examine less common complications in the woman.

Uterine artery Doppler velocimetry in high-risk pregnancies

Is uterine artery Doppler velocimetry of value in the clinical management of women at high risk of pre-eclampsia?

Why this is important

Uterine artery Doppler velocimetry is a poor predictor of pre-eclampsia as it has limited test accuracy. It is not clear how knowledge of uterine Doppler in women already identified at high risk of pre-eclampsia can influence clinical care or outcome. Studies in high risk women have involved small numbers and often mixed groups so that any benefit to a specific group could be masked.

Randomised trials of uterine artery Doppler should be carried out in women at high risk of pre-eclampsia (chronic hypertension, previous pre-eclampsia, antiphospholipid syndrome, kidney disease) and in women with multiple moderate risk factors. Trials should compare a policy of revealed uterine artery Doppler with unrevealed Doppler. Outcomes should be the consequences of severe pre-eclampsia including need for critical care, perinatal mortality and severe neonatal morbidity. Trials should be stratified for maternal risk factors.

Antihypertensives for the management of hypertension in the critical care setting

What is the most clinically effective antihypertensive agent for severe pre-eclampsia in a critical care setting?

Why this is important

The choice of antihypertensive treatment in severe hypertension in the critical care setting has evolved historically rather than scientifically and there are few useful comparisons. Dosage and route of administration vary, as does use of different routes or doses from those shown to be effective in trials.

Effective and safe control of severe hypertension is the most important aspect of critical care management, as the main cause of maternal death is the consequence of poorly controlled hypertension. Randomised controlled trials should evaluate antihypertensive treatments (labetalol, nifedipine and hydralazine) for women with severe hypertension in pregnancy in the critical care setting. Comparisons should be made between the different antihypertensives, with assessment against outcomes such as persistence of severe hypertension after completion of therapy or by the need for additional treatment, maternal side effects and the effect on the fetus and baby.

Corticosteroids in the management of HELLP syndrome

Does the use of dexamethasone in HELLP syndrome have clinical utility?

Why this is important

HELLP syndrome is a variant of severe pre-eclampsia where hypertension is less marked but where there is severe involvement of both the liver and the coagulation system. In addition to the usual complications of severe pre-eclampsia there is a risk of liver failure and bleeding.

Studies carried out to determine if steroid injections improve laboratory results have been relatively small and have not clearly shown clinically important benefits. Randomised controlled trials should be carried out in women with HELLP syndrome to assess the clinical utility of dexamethasone compared with placebo control based on outcomes associated with HELLP syndrome (delay to birth; time to hospital discharge following birth; severe maternal complications; serious neonatal complications and long-term outcomes).

Antihypertensive agents and breastfeeding

How safe are commonly used antihypertensive agents when used by women who are breastfeeding?

Why this is important

With the increasing incidence of hypertensive disorders during pregnancy, more pregnant and breastfeeding women will potentially be exposed to antihypertensive medication. Most of the relevant drugs are not licensed for use in pregnancy. For most drugs there is no information on their presence in human breast milk, or if such a presence has any clinical effect. As a result, women may either be denied effective treatment in the postnatal period or advised against breastfeeding. Studies should measure the concentration of relevant drugs and their metabolites in breast milk, taking account of drug pharmacokinetics (peak levels and elimination) and comparing neonatal behaviour and physiological variables in women using each drug with those in women who choose not to breastfeed. Studies should follow women and their babies for long enough to exclude cumulative effects and they should be large enough to provide reassurance to licensing and drug regulating authorities.

Long-term risk of cardiovascular disease

What is the long-term outcome of women with gestational hypertension?

Why this is important

Long-term follow-up of women with pre-eclampsia has shown a lifetime increased risk of serious cardiovascular complications such as stroke. Gestational hypertension is much more common than pre-eclampsia. Studies following this group of women are very limited and are not robust enough to give clear advice.

Prospective or registry studies of the long-term consequences of gestational hypertension (both isolated and recurrent) should be carried out. Outcomes should include development of hypertension, ischaemic heart disease and stroke. Studies should determine co-risk factors, particularly those amenable to intervention. Randomised controlled trials of interventions (both lifestyle and pharmacological) similar to those carried out in people considered at risk of developing type 2 diabetes, should be considered if prospective studies demonstrate significant lifetime risks.

1.5 Care pathways

Box 1: Reducing the risk of hypertensive disorders in pregnancy

Symptoms of pre-eclampsia

- Tell women to seek advice from a healthcare professional immediately if they experience any of:
  - severe headache
  - problems with vision such as blurring or flashing before eyes
  - severe pain just below ribs
  - vomiting
  - sudden swelling of face, hands or feet.

[This recommendation is adapted from 'Antenatal care: routine care for the healthy pregnant woman'
(NICE clinical guideline 62)[1]].

Lifestyle interventions

- Offer advice on rest, exercise and work in line with 'Antenatal care: routine care for the healthy pregnant woman' (NICE clinical guideline 62)[1].

Pharmacological interventions

- Do not use the following to prevent hypertensive disorders in pregnancy:
  - nitric oxide donors
  - progesterone
  - diuretics
  - low molecular weight heparin.

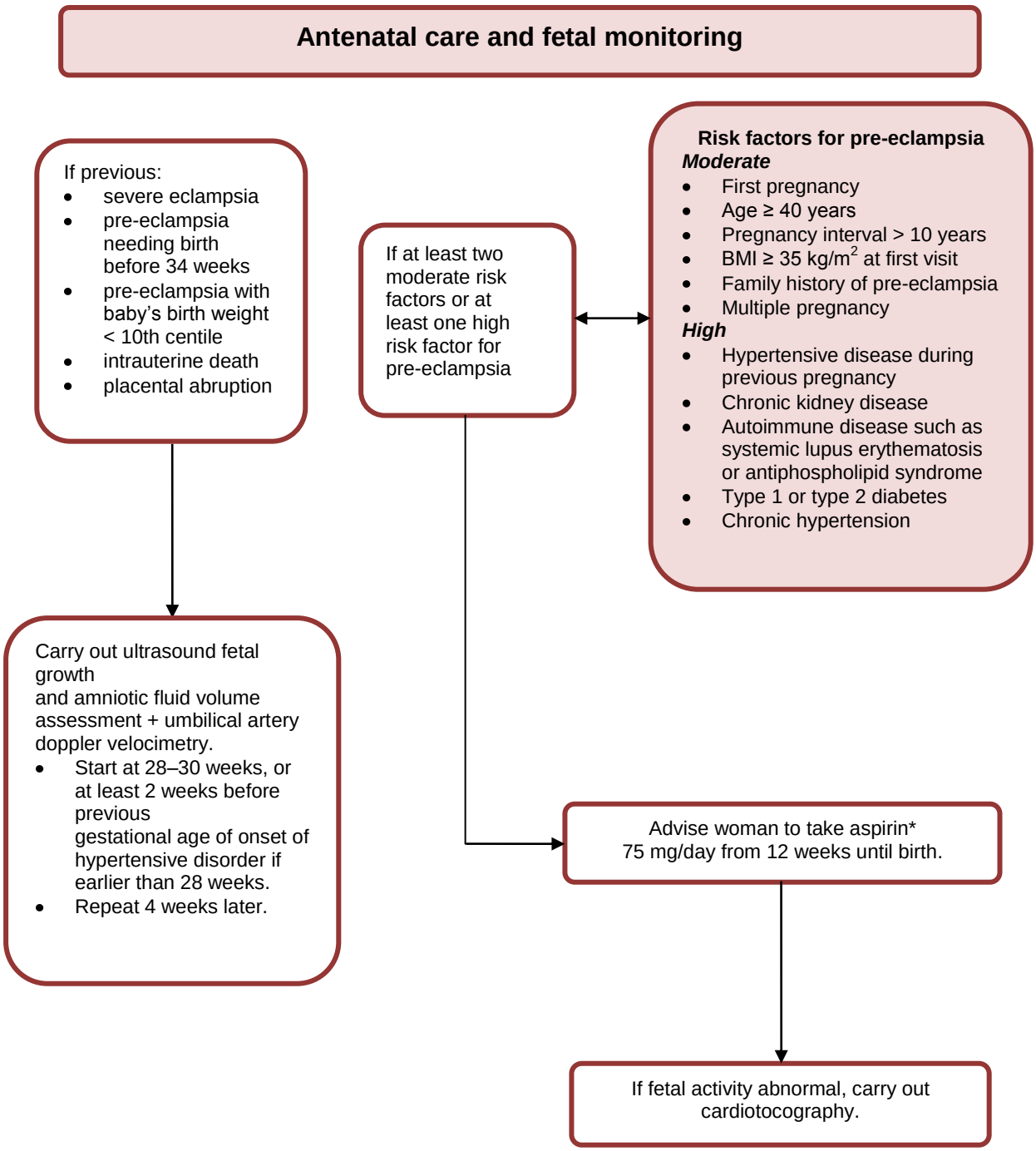
Nutritional supplements and diet

- Do not recommend the following solely with the aim of preventing hypertensive disorders during pregnancy:
  - taking supplements of magnesium, folic acid, antioxidants (vitamins C and E), fish or algal oils, or garlic
  - restricting salt intake.

Box 2: Assessment of proteinuria

- Use an automated reagent-strip reading device or a spot urinary protein:creatinine ratio to estimate proteinuria in secondary care.
- If an automated reagent-strip reading device shows proteinuria ≥ 1+, use a spot urinary protein:creatinine ratio or 24-hour urine collection to quantify proteinuria.
- Diagnose significant proteinuria if urinary protein:creatinine ratio > 30 mg/mmol or a validated 24-hour urine collection result shows > 300 mg protein.
- Where 24-hour urine collection is used to quantify proteinuria, there should be a recognised method of evaluating completeness of the sample.

Moderate and high risk of pre-eclampsia



* Unlicensed indication – obtain and document informed consent.

Chronic hypertension

Pre-pregnancy advice

Antihypertensive treatment
Tell women who are taking ACE inhibitors, ARBs or chlorothiazide:

- there is an increased risk of congenital abnormalities if ACE inhibitors or ARBs are taken during pregnancy
- there may be an increased risk of congenital abnormalities and neonatal complications if chlorothiazide is taken during pregnancy
- limited evidence shows no increased risk of congenital abnormalities with other antihypertensive treatments
- to discuss other antihypertensive treatments with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

Dietary sodium

- Encourage the woman to lower dietary sodium intake or use sodium substitute. [This recommendation is adapted from 'Hypertension: management of hypertension in adults in primary care' (NICE clinical guideline 34)[3;4]].

Antenatal care

Consultations

- Schedule additional appointments based on individual needs.

Timing of birth
If BP < 160/110 mmHg with or without antihypertensive treatment:

- do not offer birth before 37 weeks
- after 37 weeks, timing of and maternal and fetal indications for birth should be agreed between woman and senior obstetrician.

If refractory severe chronic hypertension, offer birth after course of corticosteroids (if required) has been completed.

Antihypertensive treatment

- Stop ACE inhibitors and ARBs within 2 days of notification of pregnancy and offer alternatives.
- Offer antihypertensive treatment based on pre-existing treatment, side-effect profile and teratogenicity.
- Aim for BP < 150/100 mmHg.
- If target organ damage, aim for BP < 140/90 mm Hg.
- Do not offer treatment to lower DBP to < 80 mmHg.
- If secondary chronic hypertension, offer referral to specialist in hypertensive disorders.

Fetal monitoring

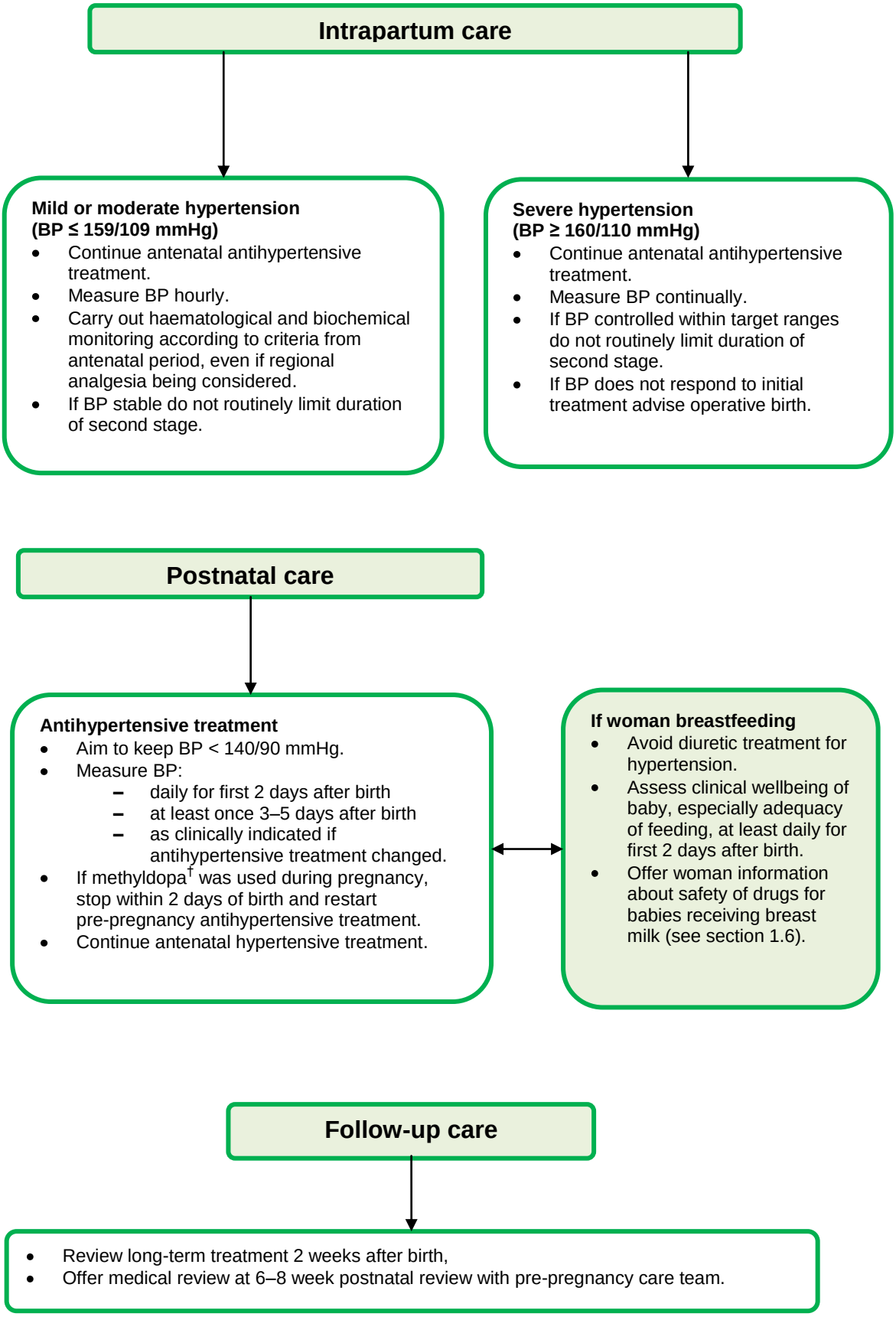
At 28–30 and 32–34 weeks carry out

- Ultrasound fetal growth and amniotic fluid volume assessment.
- Umbilical artery doppler velocimetry.

If results normal do not repeat after 34 weeks unless clinically indicated.

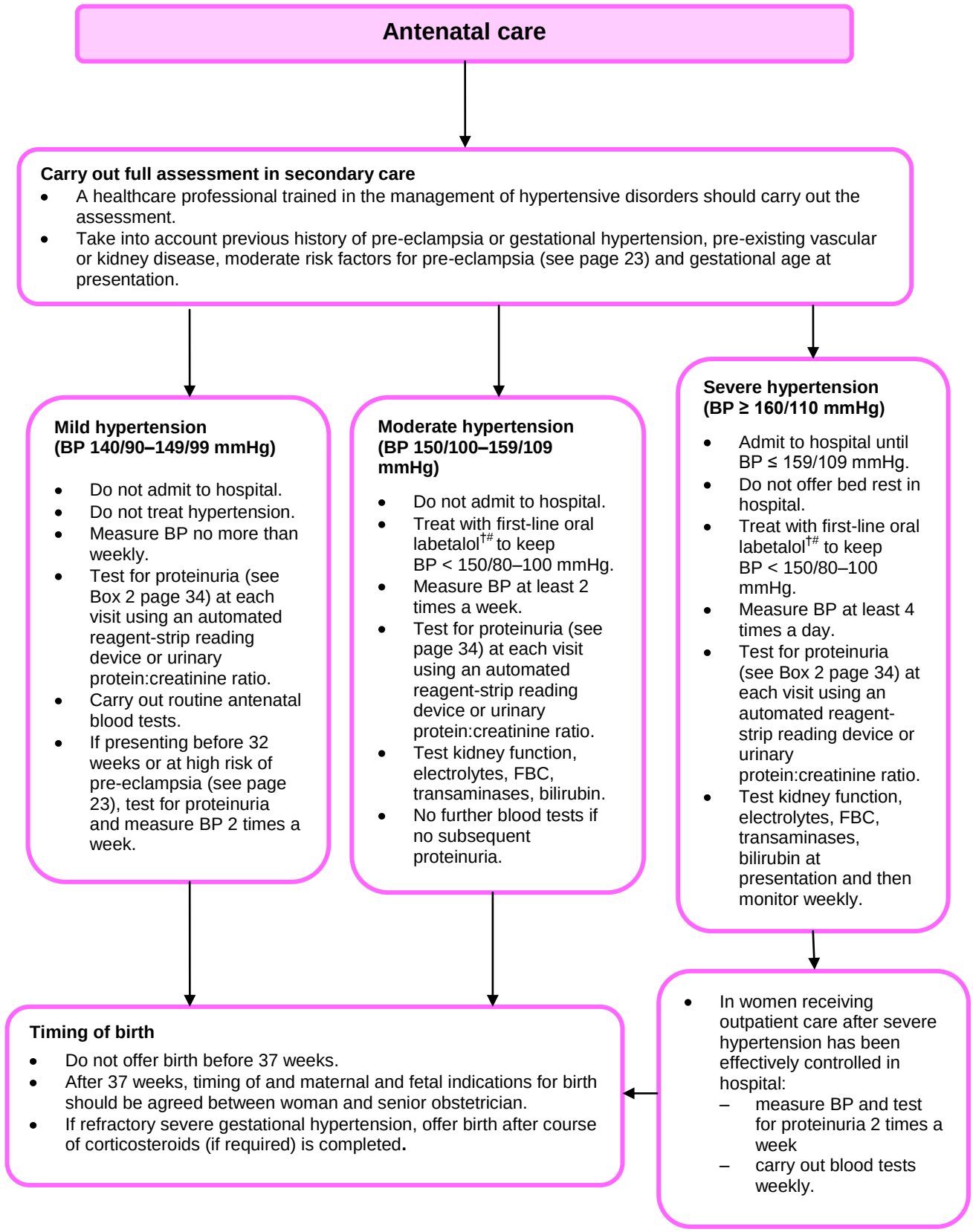
If fetal activity abnormal carry out

- Cardiotocography.

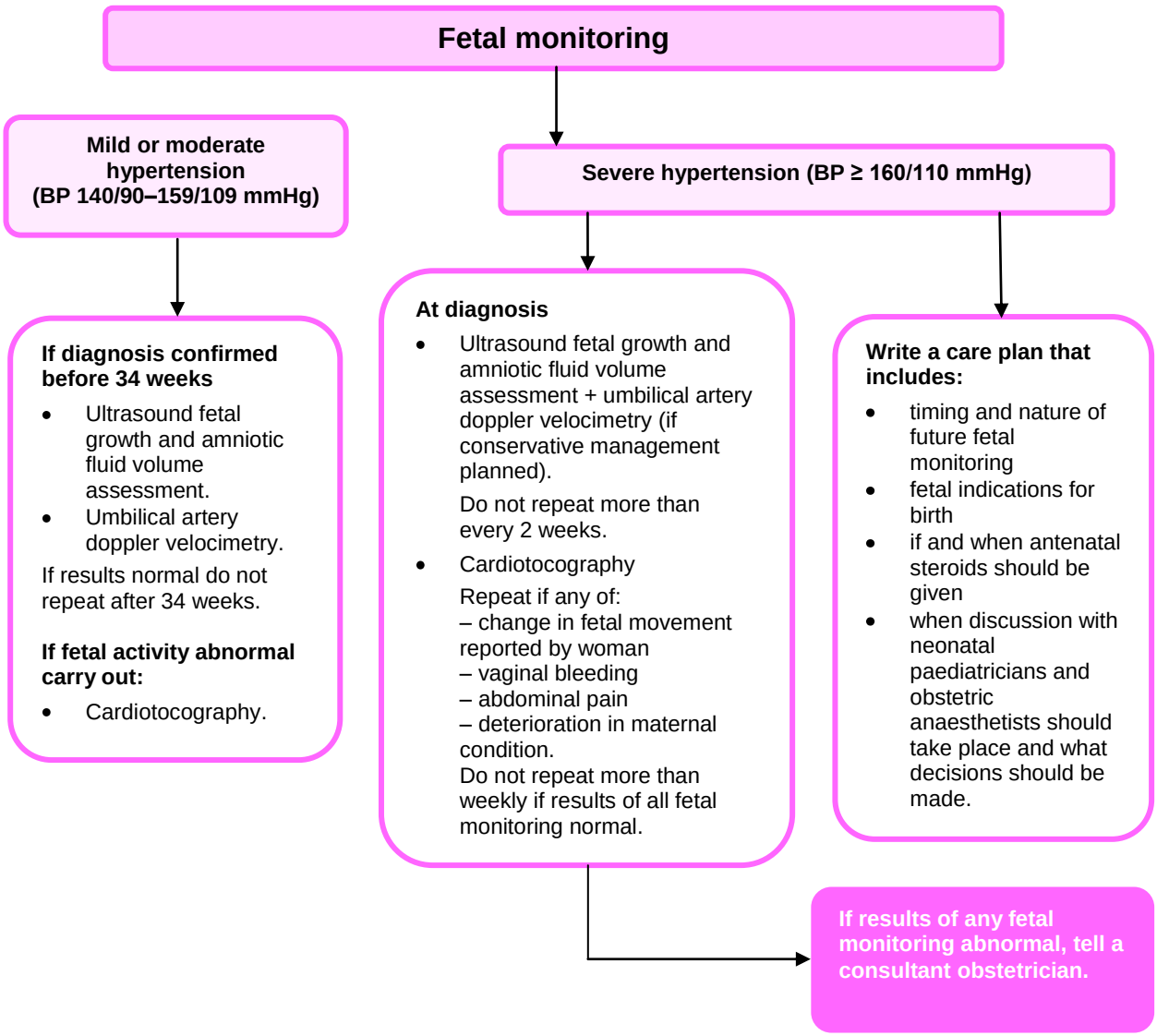


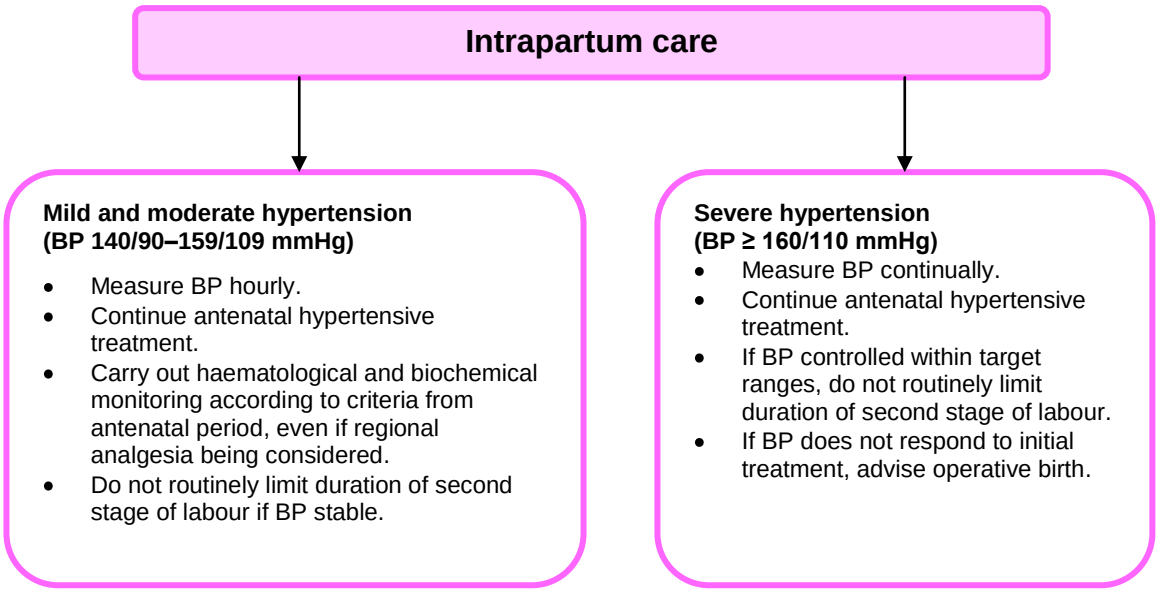
† See section 1.6 for contraindications and special warnings during pregnancy and lactation.

Gestational hypertension



Offer treatment other than labetalol† only after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine†.
† See section 1.6 for contraindications and special warnings during pregnancy and lactation.


Fetal monitoring
Mild or moderate hypertension (BP 140/90–159/109 mmHg)
Severe hypertension (BP ≥ 160/110 mmHg)
If diagnosis confirmed before 34 weeks
• Ultrasound fetal growth and amniotic fluid volume assessment.
• Umbilical artery doppler velocimetry.
If results normal do not repeat after 34 weeks.
If fetal activity abnormal carry out:
• Cardiotocography.
At diagnosis
• Ultrasound fetal growth and amniotic fluid volume assessment + umbilical artery doppler velocimetry (if conservative management planned).
Do not repeat more than every 2 weeks.
• Cardiotocography
Repeat if any of:
– change in fetal movement reported by woman
– vaginal bleeding
– abdominal pain
– deterioration in maternal condition.
Do not repeat more than weekly if results of all fetal monitoring normal.
Write a care plan that includes:
• timing and nature of future fetal monitoring
• fetal indications for birth
• if and when antenatal steroids should be given
• when discussion with neonatal paediatricians and obstetric anaesthetists should take place and what decisions should be made.
If results of any fetal monitoring abnormal, tell a consultant obstetrician.


Intrapartum care
Mild and moderate hypertension (BP 140/90–159/109 mmHg)
• Measure BP hourly.
• Continue antenatal hypertensive treatment.
• Carry out haematological and biochemical monitoring according to criteria from antenatal period, even if regional analgesia being considered.
• Do not routinely limit duration of second stage of labour if BP stable.
Severe hypertension (BP ≥ 160/110 mmHg)
• Measure BP continually.
• Continue antenatal hypertensive treatment.
• If BP controlled within target ranges, do not routinely limit duration of second stage of labour.
• If BP does not respond to initial treatment, advise operative birth.

Postnatal care

- Continue antenatal antihypertensive treatment.
- If no antenatal antihypertensive treatment, start antihypertensive treatment if BP ≥ 150/100 mmHg.
- Measure BP:
  - daily for first 2 days after birth
  - at least once 3–5 days after birth
  - as clinically indicated if antihypertensive treatment changed.
- If methyldopa† was used during pregnancy, stop within 2 days of birth.
- If BP falls to < 130/80 mmHg, reduce antihypertensive treatment.
- If BP falls to < 140/90 mmHg, consider reducing antihypertensive treatment.

If woman breastfeeding

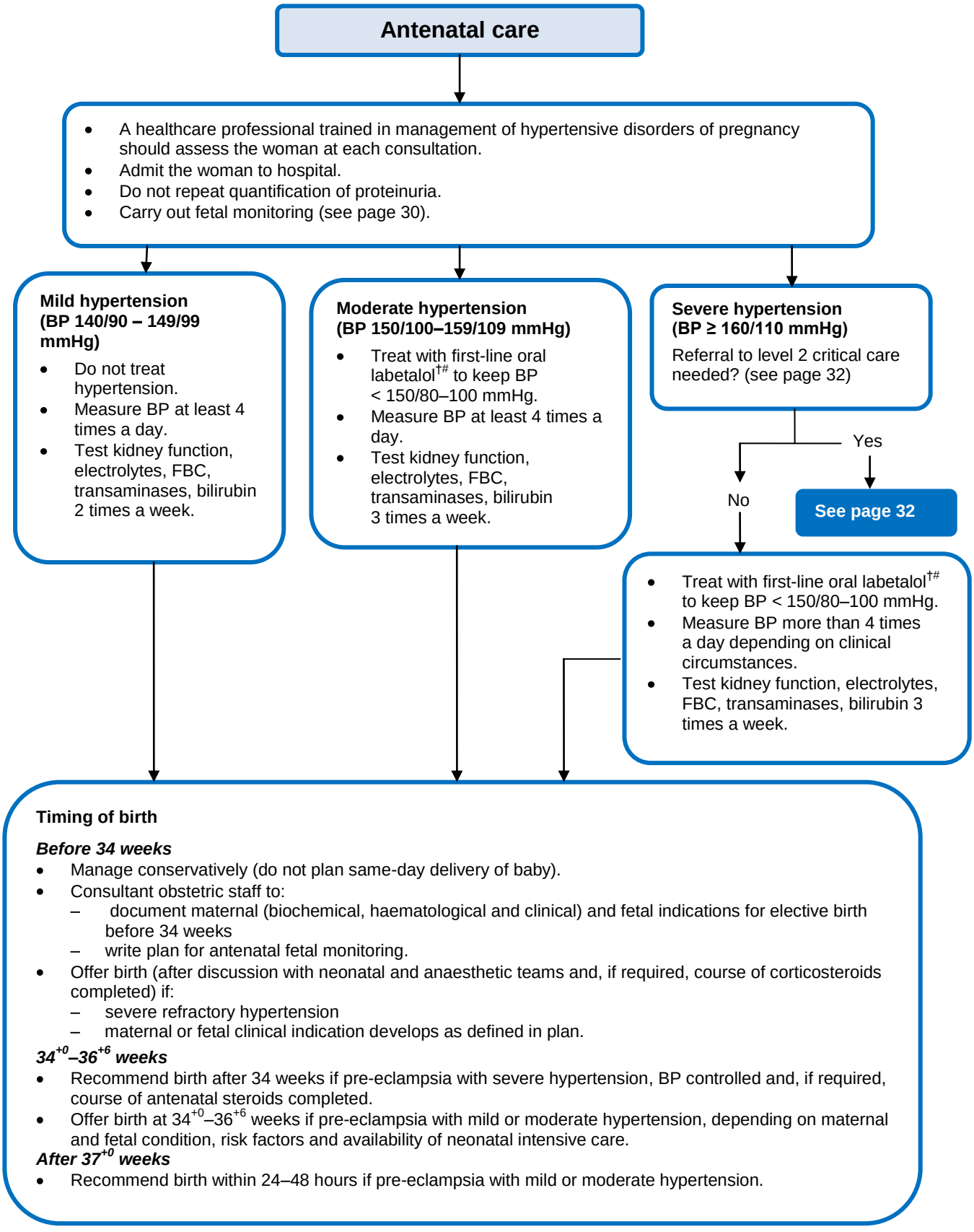
- Avoid diuretic treatment for hypertension.
- Assess clinical wellbeing of baby, especially adequacy of feeding, at least daily for first 2 days after birth.
- Offer woman information about safety of drugs for babies receiving breast milk (see Box 1 page 34).

Follow-up care

- At transfer to community care, write a care plan that includes:
  – who will provide follow-up care, including medical review if needed
  – frequency of blood pressure monitoring
  – thresholds for reducing or stopping treatment
  – indications for referral to primary care for blood pressure review.
- If antihypertensive treatment is to be continued, offer medical review 2 weeks after transfer to community care.
- Offer medical review at 6–8 week postnatal review.
- If antihypertensive treatment is to be continued after 6–8 week postnatal review, offer specialist assessment of hypertension.

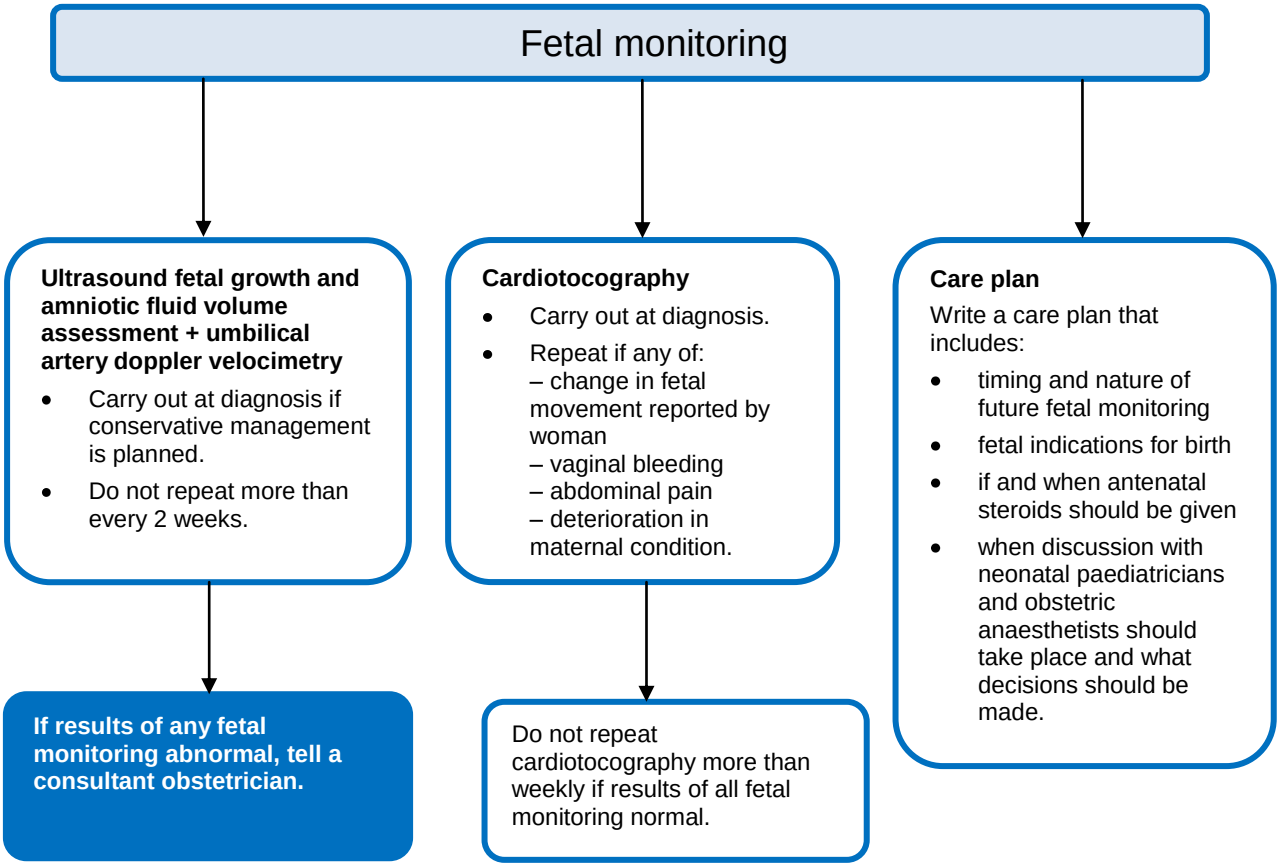
† See section 1.6 for contraindications and special warnings during pregnancy and lactation.

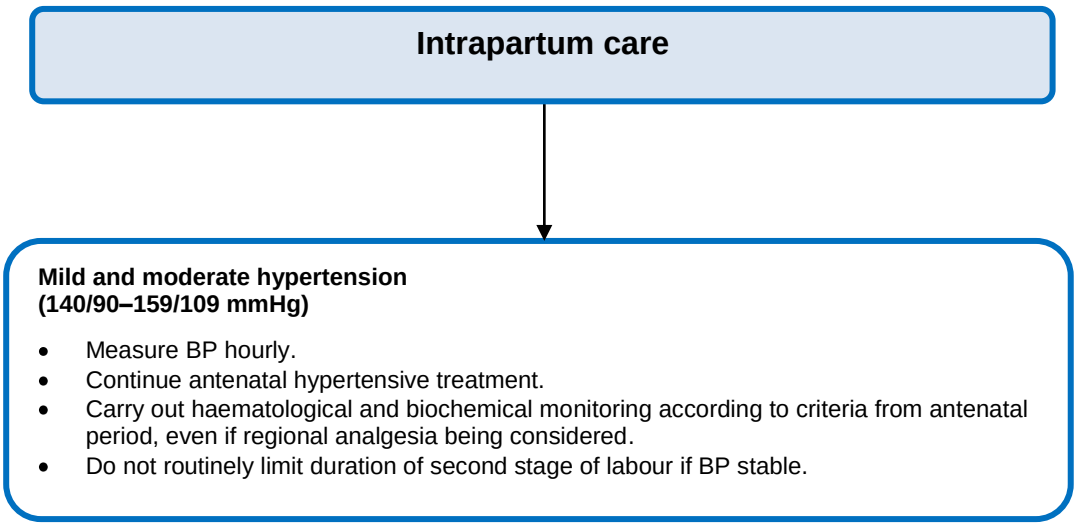
Pre-eclampsia



Offer treatment other than labetalol† only after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine†.

† See section 1.6 for contraindications and special warnings during pregnancy and lactation.


Fetal monitoring
Ultrasound fetal growth and amniotic fluid volume assessment + umbilical artery doppler velocimetry
Carry out at diagnosis if conservative management is planned.
Do not repeat more than every 2 weeks.
If results of any fetal monitoring abnormal, tell a consultant obstetrician.
Cardiotocography
Carry out at diagnosis.
Repeat if any of:
– change in fetal movement reported by woman
– vaginal bleeding
– abdominal pain
– deterioration in maternal condition.
Do not repeat cardiotocography more than weekly if results of all fetal monitoring normal.
Care plan
Write a care plan that includes:
timing and nature of future fetal monitoring
fetal indications for birth
if and when antenatal steroids should be given
when discussion with neonatal paediatricians and obstetric anaesthetists should take place and what decisions should be made.


Intrapartum care
Mild and moderate hypertension (140/90–159/109 mmHg)
Measure BP hourly.
Continue antenatal hypertensive treatment.
Carry out haematological and biochemical monitoring according to criteria from antenatal period, even if regional analgesia being considered.
Do not routinely limit duration of second stage of labour if BP stable.

Postnatal care

- If methyldopa† used to treat pre-eclampsia, stop within 2 days of birth.
- Ask the woman about severe headache and epigastric pain each time BP measured.
- If mild or moderate pre-eclampsia or after stepdown from critical care, measure platelet count, transaminases and serum creatinine 48–72 hours after birth or stepdown. Repeat as clinically indicated. Do not repeat if results normal.
- Do not measure fluid balance if creatinine within normal range after stepdown from critical care level 2.
- Offer transfer to community midwifery care if BP < 150/100 mmHg, blood test results stable or improving and no symptoms of pre-eclampsia.

If woman breastfeeding

- Avoid diuretic treatment for hypertension.
- Assess clinical wellbeing of baby, especially adequacy of feeding, at least daily for first 2 days after birth.
- Offer woman information about safety of drugs for babies receiving breast milk (see Box 1 page 34).

If no antenatal antihypertensive treatment

- Measure BP:
  - at least 4 times a day while inpatient
  - at least once 3–5 days after birth
  - on alternate days If BP abnormal 3–5 days after birth.
- If BP ≥ 150/100 mmHg, start antihypertensive treatment.

If antenatal antihypertensive treatment

- Continue antenatal antihypertensive treatment.
- Reduce antihypertensive treatment if BP falls to < 130/80 mmHg; consider reducing if BP falls to < 140/90 mmHg.
- Measure BP at least 4 times a day while inpatient.

Follow-up care and postnatal review

At transfer to community care

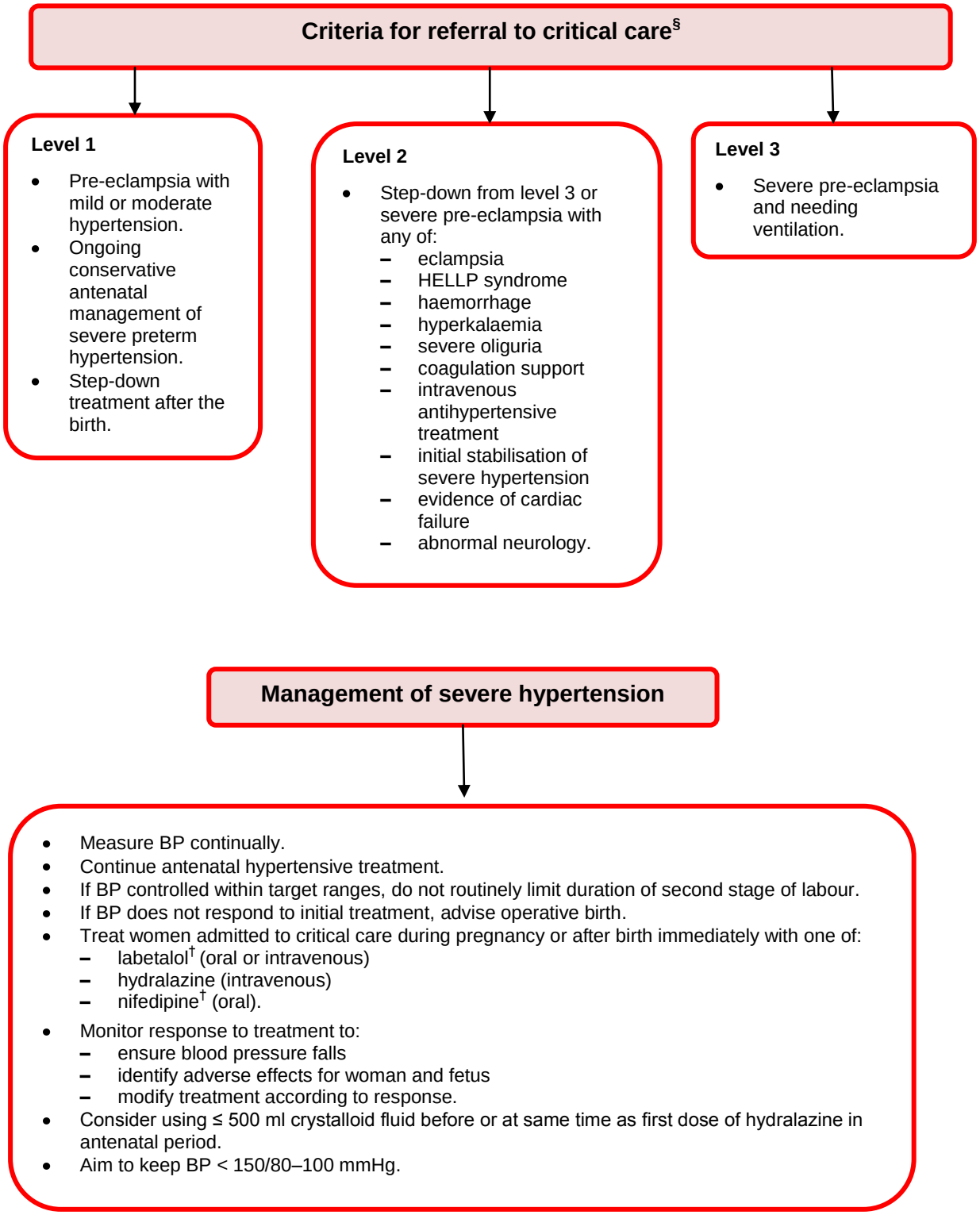
- Write a care plan that includes:
  – who will provide follow-up care, including medical review if needed
  – frequency of blood pressure monitoring
  – thresholds for reducing or stopping treatment
  – indications for referral to primary care for blood pressure review.
  – self-monitoring for symptoms.
- Measure BP every 1–2 days for up to 2 weeks after transfer to community care, until antihypertensive treatment stopped and no hyperension.
- Offer medical review if still taking antihypertensive treatment 2 weeks after transfer to community care.
- If biochemical and haematological indices improving but within abnormal range, or not improving relative to pregnancy ranges, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated.

At postnatal review (6–8 weeks after birth)

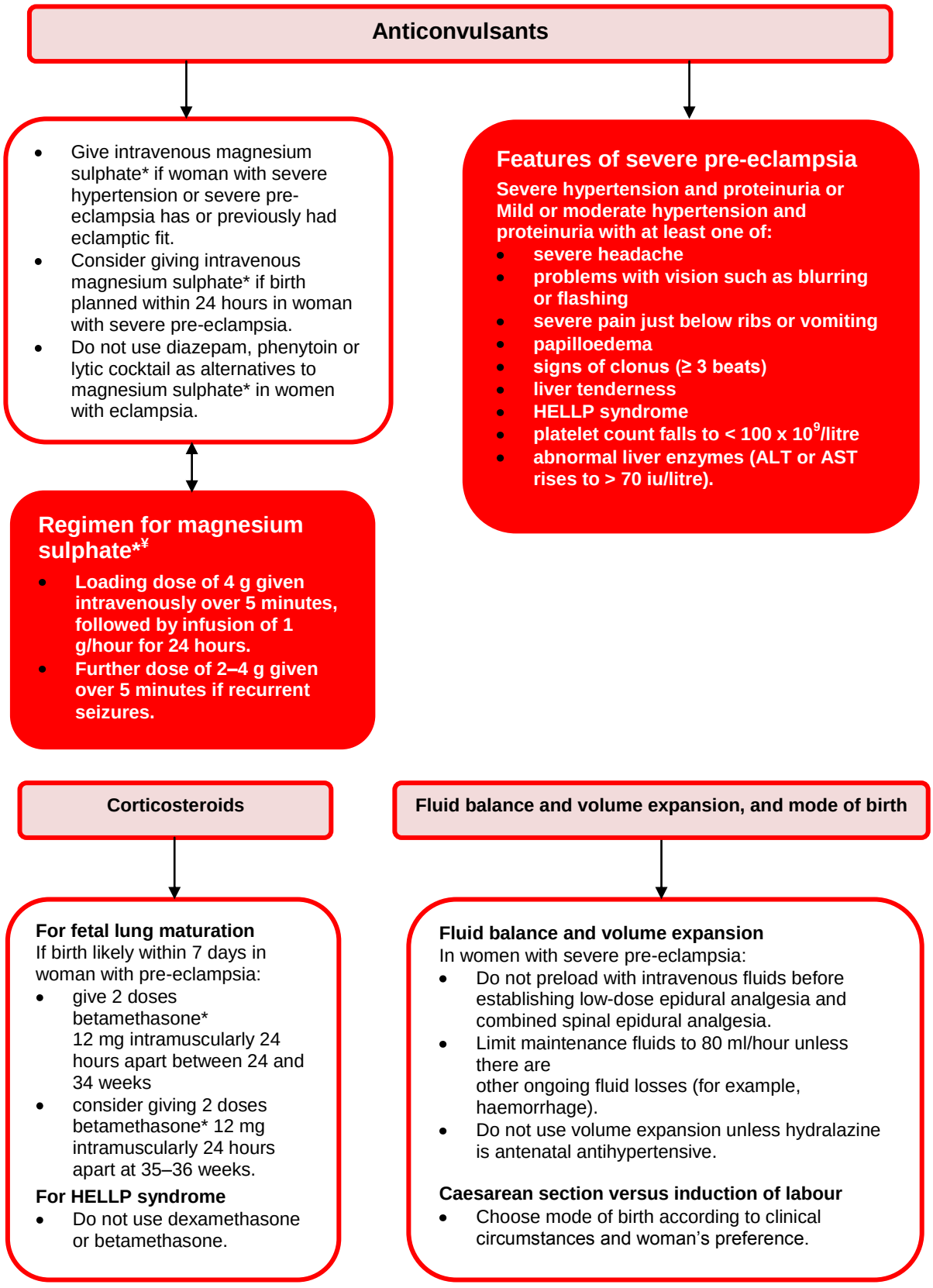
- Offer medical review.
- Offer referral for specialist assessment if antihypertensive treatment still needed.
- Repeat platelet count, transaminases and serum creatinine measurements if indicated.
- Carry out urine dipstick test.
- If proteinuria still ≥ 1+:
  – offer further review at 3 months to assess kidney function
  – consider offering referral for specialist kidney assessment.

† See section 1.6 for contraindications and special warnings during pregnancy and lactation.

Severe hypertension, severe pre-eclampsia and eclampsia in critical care



§ Adapted by the Guideline Development Group from Intensive Care Society (2002) Standards and Guidelines.
† See section 1.6 for contraindications and special warnings during pregnancy and lactation.



¥ The Eclampsia Trial Collaborative Group (1995) Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. Lancet 345:1455–63.

* Unlicensed indication – obtain and document informed consent

Box 3: Advice for women, their community midwives and primary care physicians- Breastfeeding and weight management

Breastfeeding

- Tell women that the following drugs have **no known adverse effects** on babies receiving breast milk:
  – labetalol†
  – nifedipine†
  – enalapril†
  – captopril†
  – atenolol†
  – metoprolol†.

- Tell women that there is **insufficient evidence on the safety** of the following drugs in babies receiving breast milk:
  – ARBs
  – amlodipine
  – ACE inhibitors other than enalapril† and captopril†.

Weight management

- Advise women who have had pre-eclampsia to achieve and keep BMI 18.5–24.9 kg/m^2 before next pregnancy [in line with 'Obesity: the prevention, identification, assessment and management of overweight and obesity in adults and children' (NICE clinical guideline 43)[2]].

† See section 1.6 for contraindications and special warnings during pregnancy and lactation

Long-term health risks

Future risk	Hypertensive disorder		
	Gestational hypertension	**Pre-eclampsia**	**Severe pre-eclampsia, HELLP syndrome or eclampsia**
Gestational hypertension in future pregnancy	Risk ranges from about 1 in 6 (16%) to about 1 in 2 (47%).	Risk ranges from about 1 in 8 (13%) to about 1 in 2 (53%).	
Pre-eclampsia in future pregnancy	Risk ranges from 1 in 50 (2%) to about 1 in 14 (7%).	Risk up to about 1 in 6 (16%). No additional risk if interval before next pregnancy < 10 years.	If birth was needed before 34 weeks risk is about 1 in 4 (25%). If birth was needed before 28 weeks risk is about 1 in 2 (55%).
Cardiovascular disease	Increased risk of hypertension and its complications	Increased risk of hypertension and its complications.	Increased risk of hypertension and its complications.
End-stage kidney disease		If no proteinuria and no hypertension at 6–8 week postnatal review, relative risk increased but absolute risk low. No follow-up needed.	
Thrombophilia		Routine screening not needed.	

1.6 Contraindications and special warnings

Atenolol is licensed for the treatment of hypertension and is already used widely in UK postnatal obstetric practice, but the SPCs (August 2010) advise that anticipated benefit be weighed against the possible risks of its use in the first and second trimester of pregnancy, and in women who may become pregnant or who are breastfeeding. Informed consent on the use of atenolol in these situations should be obtained and documented.

Captopril is licensed for the treatment of hypertension and is already used in UK postnatal obstetric practice, but the SPC (August 2010) advises that it is contraindicated in the second and third trimesters of pregnancy and in lactation, and that it is not recommended during the first trimester of pregnancy. Informed consent on the use of captopril in these situations should be obtained and documented.

Enalapril is licensed for the treatment of hypertension and is already used widely in UK postnatal obstetric practice, but the SPC (August 2010) advises that it is contraindicated in the second and third trimesters of pregnancy and that it is not recommended during the first trimester of pregnancy or in breastfeeding for preterm infants and for the first few weeks after delivery. Informed consent on the use of enalapril in these situations should be obtained and documented.

Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPC (August 2010) advises that it should only be used during the first trimester of pregnancy if the potential benefit outweighs the potential risk, and that breastfeeding is not recommended. Informed consent on the use of labetalol in these situations should be obtained and documented.

Methyldopa is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 2010) advises that its use in women who are, or may become, pregnant or who are breastfeeding their newborn infant requires that anticipated benefits be weighed against possible risks. Informed consent on the use of methyldopa in these situations should be obtained and documented.

Metoprolol is licensed for the treatment of hypertension and is already used widely in UK postnatal obstetric practice, but the SPCs (August 2010) advise that anticipated benefit be weighed against the possible risks of its use in women who are pregnant or breastfeeding. Informed consent on the use of metoprolol in these situations should be obtained and documented.

Nifedipine is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2010) advise that it is contraindicated in pregnancy before week 20, or that it should not be administered during the entire pregnancy or in women who may become pregnant. It also advises that nifedipine should not be used during breastfeeding. Informed consent on the use of nifedipine in these situations should be obtained and documented.

2 Development of the guideline

2.1 Hypertensive disorders of pregnancy

Hypertension during pregnancy is defined as a diastolic blood pressure of 90 mmHg or greater on two occasions more than 4 hours apart or a single diastolic blood pressure above 110 mmHg.[5] Hypertensive disorders during pregnancy occur in women with pre-existing primary or secondary chronic hypertension, and in women who develop new-onset hypertension in the second half of pregnancy.

For the purposes of this guideline, the following definitions apply.

- Chronic hypertension is hypertension that is present at the booking visit or before 20 weeks or if the woman is already taking antihypertensive medication when referred to maternity services. It can be primary or secondary in aetiology.
- Eclampsia is a convulsive condition associated with pre-eclampsia.
- HELLP syndrome is haemolysis, elevated liver enzymes and low platelet count.
- Gestational hypertension is new hypertension presenting after 20 weeks without significant proteinuria.
- Pre-eclampsia is new hypertension presenting after 20 weeks with significant proteinuria.
- Severe pre-eclampsia is pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment.
- Significant proteinuria is if there is more than 300 mg protein in a 24-hour urine collection or more than 30 mg/mmol in a spot urinary protein:creatinine sample.

The guideline definitions for chronic hypertension, gestational hypertension and pre-eclampsia are broadly consistent with those agreed by the International Society for the Study of Hypertension in Pregnancy (ISSHP).[6] The exceptions are hypertension that predates pregnancy but is not recognised before pregnancy and gestational hypertension that resolves after pregnancy, as these cannot be distinguished until the postnatal period. For the purpose of this guideline, therefore, the definition of chronic hypertension does not include new hypertension presenting after 20 weeks that does not resolve postnatally.

Although the definition of pre-eclampsia used in this guideline requires significant proteinuria, pre-eclampsia is a clinical syndrome and both clinical signs and symptoms and haematological or biochemicial abnormalities can occur in the absence of significant proteinuria.

The Guideline Development Group (GDG) has defined mild, moderate and severe hypertension to assist the development of guidance as follows:

- mild hypertension: diastolic blood pressure 90–99 mmHg, systolic blood pressure 140–149 mmHg
- moderate hypertension: diastolic blood pressure 100–109 mmHg, systolic blood pressure 150–159 mmHg
- severe hypertension: diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater.

Techniques for the measurement of blood pressure in pregnancy are described in 'Antenatal care' (NICE clinical guideline 62).[1]

Rates for chronic hypertension during pregnancy between 0.6% and 2.7% have been reported. There may be under-reporting in population datasets for this diagnosis, with the rate more likely to be nearer 2%.[7] The rate for gestational hypertension is almost certainly under-reported, with

rates between 4.2% and 7.9% recorded.[7] Both chronic hypertension and gestational hypertension can progress to pre-eclampsia. Rates for pre-eclampsia are better known, though a range of 1.5% to 7.7% has been reported.[8-13] The rate depends on the distribution of parity in the population: the rate for primigravid women is 4.1% and in women in their second pregnancy 1.7%.[14] It is likely that up to 10% of pregnancies are complicated by hypertensive disorders and there is evidence that the rate may be increasing.

Hypertensive disorders during pregnancy carry risks for the woman and the baby. Although the rate of eclampsia in the UK appears to have fallen,[15] hypertension in pregnancy remains one of the leading causes of maternal death in the UK, Europe and elsewhere.[16;17] Detailed enquiries have examined standards of care, and substandard care (where different management might have been expected to prevent death) has been identified in the majority of cases. These failures of care have not just occurred in the critical care environment.

Hypertensive disorders during pregnancy may result in substantial maternal morbidity, and maternal death is the tip of the iceberg. A UK study reported that one-third of severe maternal morbidity was a consequence of hypertensive conditions,[18] and a study conducted in the USA found that over half of admissions for acute kidney failure, one-quarter of admissions for coagulopathy and nearly one-third of admissions for ventilation or cerebrovascular disorders occurred in women with hypertensive disorders.[19] A study from one region of the UK reported that 1 in 20 (5%) women with severe pre-eclampsia or eclampsia was admitted to intensive care.[20]

More recently, the long-term consequences for women with a diagnosis of hypertension during pregnancy have become clear, in particular chronic hypertension and an increase in lifetime cardiovascular risk.[21]

The standard pattern of antenatal care developed in the 1920s was largely aimed at detection of pre-eclampsia. Over recent years, the lack of good predictive tests and of preventative treatment has resulted in surveillance aimed at early detection and assessment of hypertensive disease in pregnancy, the consequences of which are poorly understood for women and the maternity service.

Hypertensive disorders also carry a risk for the baby. In the most recent UK perinatal mortality report, about 1 in 20 (5%) stillbirths in infants without congenital abnormality occurred in women with pre-eclampsia.[22] While this may be an improvement from the late 1990s (7%),[23] it still represents a significant burden. A similar trend in the stillbirth rate has been seen in Sweden.[24] Ten percent of women with severe pre-eclampsia give birth before 34 weeks.[14] The contribution of pre-eclampsia to the overall preterm birth rate is substantial: 1 in 250 (0.4%) women in their first pregnancy will give birth before 34 weeks as a consequence of pre-eclampsia[14] and 8–10% of all preterm births result from hypertensive disorders.[25] Half of women with severe pre-eclampsia give birth preterm.[26]

Small-for-gestational-age (SGA) babies (mainly because of intrauterine growth restriction (IUGR) arising from placental disease) are common, with 20–25% of preterm births and 14–19% of term births in women with pre-eclampsia being less than the tenth centile of birthweight for gestation.[26]

There is national guidance on the care of women with severe pre-eclampsia or eclampsia[27] and on screening for hypertensive disorders during pregnancy.[1] However, there has been no guidance on the assessment and care of women and their babies after a diagnosis of hypertension (including the use of antihypertensive treatment) or on maternity care for women with chronic hypertension.

This clinical guideline contains recommendations for the diagnosis and management of hypertensive disorders during pregnancy in the antenatal, intrapartum and postnatal periods. It includes recommendations for women with chronic hypertension who wish to conceive and recommendations for advice to women after a pregnancy complicated by hypertension. At its core is an assumption that recommendations and advice, including the generally poor quality of the evidence on which they are based, and the need to balance maternal and perinatal risk, will be fully discussed with women and their families.

2.2 Aim and scope of the guideline

This clinical guideline concerns the management of hypertensive disorders in pregnancy and their complications from preconception to the postnatal period. For the purpose of this guideline, 'pregnancy' includes the antenatal, intrapartum and postpartum (6 weeks after birth) periods.

The guideline has been developed with the aim of providing guidance in the following areas:

- information and advice for women who have chronic hypertension and are pregnant or planning to become pregnant
- information and advice for women who are pregnant and at increased risk of developing hypertensive disorders of pregnancy
- management of pregnancy with chronic hypertension
- management of pregnancy in women with gestational hypertension
- management of pregnancy for women with pre-eclampsia before admission to critical care level 2 setting
- management of pre-eclampsia and its complications in a critical care setting
- information, advice and support for women and healthcare professionals after discharge to primary care following a pregnancy complicated by hypertension
- care of the fetus during pregnancy complicated by a hypertensive disorder.

The following areas are specifically excluded from the guideline:

- the detection of hypertension during pregnancy (this is covered in 'Antenatal care' (NICE clinical guideline 62)[1]
- screening strategies for risk factor identification.

Further information about the areas covered in the guideline is available in the 'scope' of the guideline (reproduced in Appendix A).

2.3 For whom is the guideline intended?

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England, Wales and Northern Ireland, in particular:

- healthcare professionals involved in the care of women with hypertensive disorders during pregnancy and their newborn babies (including GPs, nurses, midwives, obstetricians, cardiology physicians and neonatal paediatricians)
- those responsible for commissioning and planning healthcare services, including primary care trust commissioners, Health Commission Wales commissioners, and public health and trust managers
- women with hypertensive disorders of pregnancy and their families.

A version of this guideline for women with hypertensive disorders of pregnancy and the public is available from the NICE website (www.nice.org.uk/CG107) or from NICE publications on 0845 003 7783 or email publications@nice.org.uk (and quote reference N1739).

2.4 Other relevant documents

This guideline is intended to complement other existing and proposed works of relevance, including the following guidance published by NICE:

- 'Antenatal care', NICE clinical guideline 62[1]
- 'Intrapartum care', NICE clinical guideline 55[28]
- 'Postnatal care', NICE clinical guideline 37[29]
- 'Induction of labour', NICE clinical guideline 70[30]
- 'Caesarean section', NICE clinical guideline 13[31]
- 'Hypertension', NICE clinical guideline 34[3,4]
- 'Diabetes in pregnancy', NICE clinical guideline 63[32]

- 'Obesity', NICE clinical guideline 43[2]
- 'Chronic kidney disease', NICE clinical guideline 73[33]
- 'Smoking cessation services', NICE public health guidance 10[34]
- 'Maternal and child nutrition', NICE public health guidance 11[35]
- 'How to stop smoking in pregnancy and following childbirth', NICE public health guidance 26[36]
- 'Weight management before, during and after pregnancy', NICE public health guidance 27.[37]

2.5 Who has developed the guideline?

The guideline was developed by a multi-professional and lay GDG convened by the National Collaborating Centre for Women's and Children's Health (NCC-WCH). Membership included:

- four obstetricians
- two midwives
- an obstetric physician
- an obstetric anaesthetist
- a neonatal paediatrician
- a GP
- a pharmacist
- two patient/carer members.

NCC-WCH staff provided methodological support for the guideline development process, undertook systematic searches, retrieved and appraised the evidence, developed health economic models, and wrote successive drafts of the guideline.

Four external advisers were appointed by the GDG to advise on anaesthesia, obstetric critical care, and methods for detection and quantification of urinary protein.

All GDG members' and external advisers' potential and actual conflicts of interest were recorded on declaration forms provided by NICE (summarised in Appendix B). None of the interests declared by GDG members constituted a material conflict of interest that would influence recommendations developed by the GDG.

Organisations with interests in the management of hypertensive disorders during pregnancy and their complications from preconception to the postnatal period were encouraged to register as stakeholders for the guideline. Registered stakeholders were consulted throughout the guideline development process. The types of organisations eligible to register as stakeholders included:

- national patient and carer organisations that directly or indirectly represent interests of women with hypertensive disorders of pregnancy and their families
- national organisations that represent healthcare professionals who provide services for women with hypertensive disorders of pregnancy
- companies that manufacture preparations and/or products used in the management of hypertensive disorders during pregnancy
- providers and commissioners of health services in England, Wales and Northern Ireland
- statutory organisations such as the Department of Health and the Welsh Assembly Government
- research organisations that have undertaken nationally recognised research in relation to the topics covered in the guideline.

A list of registered stakeholder organisations for this guideline is presented in Appendix C.

2.6 Guideline development methodology

This guideline was commissioned by NICE and developed in accordance with the process outlined in successive editions of 'The guidelines manual' (see www.nice.org.uk/guidelinesmanual). Table 2.1 summarises the key stages of the process and which version of 'The guidelines manual' was followed at each stage. In accordance with NICE's Equality Scheme (see www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp), ethnic and cultural considerations and factors relating to disabilities were considered by the GDG at every stage of the process and addressed specifically in individual recommendations where relevant.

Table 2.1 Stages in the NICE guideline development process and versions of the 'The guidelines manual' followed at each stage

Stage	2007 version	2009 version
Scoping the guideline (determining what the guideline would and would not cover)	✓	
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution, etc.)	✓	
Forming and running the GDG	✓	
Developing clinical questions	✓	
Identifying evidence	✓	
Reviewing and grading evidence	✓	
Incorporating health economics	✓	
Making group decisions and reaching consensus	✓	
Linking guidance to other NICE guidance	✓	
Creating guideline recommendations	✓	
Writing the guideline	✓	
Stakeholder consultation on the draft guideline		✓
Finalising and publishing the guideline (including pre-publication check)		✓
Declaration of interests	✓	✓

Developing clinical questions and identifying evidence

The GDG formulated clinical questions based on the scope (see Appendix D). These formed the starting point for subsequent evidence reviews. Relevant published evidence to answer the clinical questions was identified by applying systematic search strategies (see Appendix E) to the following databases: Medline (1950 onwards), Embase (1980 onwards), Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 onwards), and three Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluation Database (NHS EED). None of the searches was limited by date or language of publication (although publications in languages other than English were not reviewed). Generic and specially developed search filters were used to identify particular study designs, such as randomised controlled trials (RCTs). There was no systematic attempt to search grey literature (conferences, abstracts, theses and unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 20 May 2009.

Reviewing and grading evidence

Evidence relating to clinical effectiveness was reviewed and graded using the hierarchical system presented in Table 2.2. This system reflects the susceptibility to bias inherent in particular study designs.

The type of clinical question dictates the highest level of evidence that may be sought. In assessing the quality of evidence, each study was assigned a quality rating coded as '++', '+' or '−'. For issues of therapy or treatment, the highest possible evidence level (EL) is a well-conducted systematic review or meta-analysis of RCTs (EL = 1++) or an individual RCT (EL = 1+). Studies of poor quality were rated as '−'. Studies rated as '−' should not be used as a basis for making a recommendation, but they may be used to inform recommendations. For issues of prognosis, the highest possible level of evidence is a cohort study (EL = 2).

Table 2.2 Levels of evidence for intervention studies

Level	Source of evidence
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies; high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding , bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies (e.g. case reports, case series)
4	Expert opinion, formal consensus

For each clinical question, the highest available level of evidence was sought. Where appropriate, for example if a systematic review with or without a meta-analysis or an RCT was identified to answer a question, studies of a weaker design were not considered. Where such studies were not identified, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the effectiveness (accuracy) of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients (women or their babies) and the outcome of disease was required, evidence from RCTs or cohort studies was optimal. For studies evaluating the accuracy of a diagnostic test, sensitivity, specificity, positive predictive values (PPVs) and negative predictive values (NPVs) were calculated or quoted where possible (see Table 2.3). Likelihood ratios (LRs) were also quoted where reported.

Table 2.3 '2 × 2' table for calculation of diagnostic accuracy parameters

	Reference standard positive	Reference standard negative	Total
Test positive	a (true positive)	b (false positive)	a+b
Test negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d = N (total number of tests in study)

Sensitivity = a/(a+c), specificity = d/(b+d), PPV = a/(a+b), NPV = d/(c+d)

The hierarchical system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting accuracy of diagnostic tests. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy of evidence that takes into account various factors likely to affect the validity of such studies (see Table 2.4).

Some studies were excluded from the reviews after obtaining copies of then because they did not meet inclusion criteria specified by the GDG (see Appendix F). Clinical evidence from included studies was extracted into evidence tables for each question (see Appendix G), and a brief summary of each study was included in the guideline text. Where possible, dichotomous outcomes are presented as relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs), and continuous outcomes are presented as mean differences with 95% CIs or standard deviations (SDs).

The body of evidence identified for each clinical question was synthesised qualitatively in clinical evidence statements. Quantitative synthesis (meta-analysis) was not undertaken for this guideline because there were no clinical questions for which sufficient numbers of similar studies were identified to merit such analysis.

Table 2.4 Levels of evidence for studies of the accuracy of diagnostic tests

Level	Type of evidence
Ia	Systematic review (with homogeneity)[a] of level-1 studies[b]
Ib	Level-1 studies[b]
II	Level-2 studies[c]; systematic reviews of level-2 studies
III	Level-3 studies[d]; systematic reviews of level-3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] Homogeneity means there are minor or no variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] Level-1 studies are studies that use a blind comparison of the test with a validated reference standard ('gold' standard) in a sample of patients that reflects the population to whom the test would apply.

[c] Level-2 studies are studies that have only one of the following:
- narrow population (the sample does not reflect the population to whom the test would apply)
- use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- the comparison between the test and reference standard is not blind
- case–control studies.

[d] Level-3 studies are studies that have at least two or three of the features listed above.

Incorporating health economics

The aims of the health economic input to the guideline were to inform the GDG of potential economic issues relating to the management of hypertensive disorders during pregnancy and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality-adjusted life years; QALYs), harms and costs of various care options.

The GDG prioritised a number of clinical questions where it was thought that economic considerations would be particularly important in formulating recommendations. Systematic searches for published economic evidence were undertaken for these questions. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation.[38] Reviews of the (very limited) relevant published economic literature are presented alongside the clinical effectiveness reviews or as part of appendices detailing original economic analyses (see below).

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline, the areas prioritised for economic analysis were as follows:

- cost effectiveness of using aspirin prophylactically to prevent pre-eclampsia and its complications in women at risk of developing pre-eclampsia (see Appendix H)
- cost effectiveness of immediate birth by planned induction of labour compared with expectant management for women with mild to moderate gestational hypertension at 37–40 weeks (see Appendix I)
- cost effectiveness of immediate birth by planned induction of labour compared with expectant management for women who have pre-eclampsia with mild or moderate hypertension at 34–37 weeks (see Appendix J)
- cost effectiveness of using a '1+' dipstick urinalysis threshold compared with a '2+' dipstick urinalysis threshold in screening for proteinuria in women with gestational hypertension (see Appendix K)
- cost effectiveness of automated urinalysis compared with visual urinalysis in screening for proteinuria in women with gestational hypertension (see Appendix L)
- cost effectiveness of quantifying proteinuria in women with gestational hypertension (see Appendix M).

GDG interpretation of the evidence and creating recommendations

For each clinical question, recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the GDG to agree clinical and, where appropriate, cost-effectiveness evidence statements. Statements summarising the GDG's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process.

In areas where no substantial clinical research evidence was identified, the GDG considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on GDG consensus in relation to the likely cost-effectiveness implications of the recommendations. The GDG also identified areas where evidence to answer their clinical questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process, formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously. The GDG identified ten 'key priorities for implementation' (key recommendations) and five high-priority research recommendations. The key priorities for implementation were those recommendations likely to have the biggest impact on patient care and patient outcomes in the NHS as a whole; they were selected using a variant of the nominal group technique (see the NICE guidelines manual). The priority research recommendations were selected in a similar way.

Stakeholder involvement in the guideline development process

Registered stakeholder organisations were invited to comment on the draft scope of the guideline and on the draft guideline. Stakeholder organisations were also invited to undertake a pre-publication check of the final guideline to identify factual inaccuracies. The GDG carefully considered and responded to all comments received from stakeholder organisations. The comments and responses, which were reviewed independently for NICE by a Guidelines Review Panel, are published on the NICE website.

2.7 Specific considerations for this guideline

Where the evidence supported it, the GDG made separate recommendations for women with chronic hypertension, gestational hypertension and pre-eclampsia.

For this guideline, the effectiveness of interventions was assessed against the following maternal, neonatal and infant outcomes:

- maternal outcomes:
  - maternal death
  - pre-eclampsia
  - severe pre-eclampsia, eclampsia and HELLP syndrome
  - maternal complications (CVA, cerebral haemorrhage, myocardial infarction, kidney failure, placental abruption and pulmonary oedema)
  - admission to a high-dependency unit (HDU) or intensive care unit (ICU)
  - need for antihypertensive medications
  - maternal QALYs
- neonatal and infant outcomes:
  - perinatal mortality, neonatal death and fetal death
  - neonatal complications (hypoglycaemia, hypothermia, hypotension, feeding difficulties, jaundice and neonatal bradycardia)
  - admission to a neonatal intensive care unit (NICU)
  - SGA and IUGR
  - preterm birth before 34 weeks
  - preterm birth (before 37 weeks)

- short-term evidence of hypoxia (cord pH, hypoxic ischaemic encephalopathy, need for resuscitation at birth in a term baby)
- long-term complications (neurodevelopment)
- neonatal QALYs.

2.8 Schedule for updating the guideline

Clinical guidelines commissioned by NICE are published with a review date 3 years from the date of publication. Reviewing may begin before 3 years have elapsed if significant evidence that affects guideline recommendations is identified sooner.

In this revised reprint, the wording of the recommendations to avoid the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and chlorothiazide have been revised (see Sections 1.1, 1.2 and 4.2.1). The care pathway has also been revised to reflect the changes to the recommendations (see Section 1.5).

3 Reducing the risk of hypertensive disorders in pregnancy

3.1 Introduction

Some women entering pregnancy have pre-existing risk factors for the development of hypertensive disorders during that pregnancy. These may be pre-existing medical diseases, such as diabetes, chronic hypertension, chronic kidney disease or autoimmune disease, or the occurrence of hypertensive disease during a previous pregnancy. Other factors produce more modest increases in risk, such as obesity, primiparity, age, a family history of hypertensive disorders of pregnancy, or a blood pressure at the higher end of the normal range for age.[39;40]

This section considers whether there are interventions that could be implemented before or during pregnancy that would remove or reduce the risk of hypertensive disease during pregnancy.

3.2 Antiplatelet agents

Clinical effectiveness

A Cochrane systematic review and a meta-analysis of individual-patient data were identified. The Cochrane systematic review focused specifically on the reduction of risk of pre-eclampsia.[41] [EL = 1+] In order to assess the effectiveness of various dosages of aspirin for the prevention of pre-eclampsia, a subgroup analysis by dose was conducted for the guideline using studies included in the Cochrane systematic review.[41] The meta-analysis of individual-patient data on risk reduction for pre-eclampsia with antiplatelet agents provided subgroup analysis by risk factor.[42] [EL = 1++] A further RCT focused on a specific population of women with the converting enzyme DD and a history of pre-eclampsia.[43] [EL = 1+] A Health Technology Assessment (HTA) report[39] was also identified but was not included in the guideline review of clinical effectiveness because all the individual studies contained in the report were considered in the other publications listed above.

A Cochrane systematic review of 59 RCTs involving 37 560 women was conducted to determine the effectiveness of antiplatelet agents (mainly aspirin) in reducing the risk of pre-eclampsia and its complications.[41] [EL = 1+] Comparisons were made between any antiplatelet agent (such as low-dose aspirin or dipyridamole) with placebo or no antiplatelet agent, irrespective of dose, duration of therapy, mode of administration and whether used alone or in combination with another agent.

Thirty-four studies included in the Cochrane review evaluated the prevention of gestational hypertension ($n = 20\,701$). No statistically significant difference was found in the incidence of gestational hypertension in women receiving antiplatelet agents compared with women receiving placebo or no antiplatelet agents (RR 0.95; 95% CI 0.88 to 1.03). Pre-eclampsia was evaluated in 43 studies ($n = 32\,590$) and the pooled analysis showed that antiplatelet agents were associated with a statistically significant reduction in the risk of pre-eclampsia (RR 0.83; 95% CI 0.77 to 0.89). In 38 of the 43 included studies, the intervention was high- or low-dose aspirin. Antiplatelet agents were associated with a statistically significant reduction in the risks of

preterm birth before 37 weeks (RR 0.92; 95% CI 0.88 to 0.97) and fetal and neonatal deaths (RR 0.86; 95% CI 0.76 to 0.98).

A subgroup analysis of maternal risk for gestational hypertension and pre-eclampsia was conducted. Maternal risk was divided into moderate and high risk. High risk was defined as chronic hypertension without superimposed pre-eclampsia or normotension with one or more of the following: previous severe pre-eclampsia, diabetes, chronic hypertension, kidney disease or autoimmune disease. Moderate risk was defined as any other risk factor, in particular first pregnancy, a mild rise in blood pressure and no proteinuria, abnormal uterine artery Doppler velocimetry, positive roll-over test, body mass index (BMI) multiple pregnancy, a family history of pre-eclampsia or being a teenager.

The subgroup analysis showed that antiplatelet agents had no statistically significant effect in moderate-risk women (22 studies, $n = 10\,862$) for reducing the risk of gestational hypertension (RR 1.00; 95% CI 0.92 to 1.08), whereas they were associated with a statistically significantly lower risk of gestational hypertension in high-risk women (12 studies, $n = 838$, RR 0.54; 95% CI 0.41 to 0.70).

Antiplatelet agents were associated with statistically significant reductions in the risk of pre-eclampsia in moderate-risk women and in high-risk women (moderate-risk women: 25 studies, $n = 28\,469$, RR 0.86; 95% CI 0.79 to 0.95; high-risk women: 18 studies, $n = 4121$, RR 0.75; 95% CI 0.66 to 0.85).

Another subgroup analysis was conducted by dose of the antiplatelet agent, specifically low-dose aspirin (defined as 75 mg/day or less), higher dose aspirin (defined as more than 75 mg aspirin per day), and a third category (more than 75 mg aspirin per day plus dipyridamole). Nineteen studies ($n = 16\,095$) evaluated the effect of low-dose aspirin on gestational hypertension. The result of the pooled analysis showed no statistically significant effect (RR 0.98; 95% CI 0.90 to 1.08) whereas a higher dose of aspirin, evaluated in nine studies ($n = 800$), was associated with a statistically significant reduction in the risk of gestational hypertension (RR 0.67; 95% CI 0.49 to 0.92). Three studies ($n = 382$) investigated the effect of more than 75 mg aspirin plus dipyridamole and analysed together they showed a statistically significant reduction in risk (RR 0.70; 95% CI 0.51 to 0.95).

Similarly, the Cochrane systematic review reported a statistically significant effect in women receiving low-dose aspirin and those receiving a higher dose of aspirin (more than 75 mg) on the incidence of pre-eclampsia compared with women receiving placebo or no treatment (low dose: 21 studies, $n = 26\,984$, RR 0.88; 95% CI 0.81 to 0.95; higher dose: 17 studies, $n = 5061$, RR 0.64; 95% CI 0.51 to 0.80). The combined effect across five studies ($n = 296$) evaluating more than 75 mg aspirin plus dipyridamole showed a statistically significant reduction in risk among women receiving this intervention compared with women receiving placebo or no treatment (RR 0.30; 95% CI 0.15 to 0.60).

A further subgroup analysis by dose of aspirin (mg/day) was conducted for this guideline by the NCC-WCH team to evaluate the optimal dosage. The subgroups considered were 60 mg, 75 mg, 100 mg and 150 mg/day. The group taking 60 mg aspirin per day showed a marginally statistically significant reduction in risk of developing pre-eclampsia (14 studies, RR 0.92; 95% CI 0.84 to 1.00) and the group taking 75 mg aspirin per day showed a statistically significant reduction in risk (eight studies, RR 0.65; 95% CI 0.51 to 0.83). The groups taking 100 mg/day and 150 mg/day showed no statistically significant reduction (100 mg group: 13 studies, RR 0.71; 95% CI 0.50 to 1.02; 150 mg group: three studies, RR 0.95; 95% CI 0.67 to 1.35), although these higher dose groups may have been underpowered to detect a difference owing to the small numbers of studies.

The Cochrane systematic review[41] included two studies that followed up children at 12–18 months. One study reported no statistically significant difference in long-term adverse effects at 12–18 months between children in the treatment and the placebo groups. The other study reported a statistically significantly higher risk of fine or gross motor problems in the treatment group but it was noted that the study was unblinded and 27% of children were lost to follow up.

A meta-analysis using individual-patient data assessed the effectiveness of antiplatelet agents (mainly aspirin) in risk reduction for pre-eclampsia;[42] [EL = 1++] this analysis included 32 217

women and their 32 819 babies. Overall, the analysis showed a statistically significant reduction in risk of developing pre-eclampsia (RR 0.90; 95% CI 0.84 to 0.97). The data from this study suggest that one case of pre-eclampsia would be prevented for every 114 women treated with antiplatelet agents. In addition to the 10% reduction in pre-eclampsia in high-risk women receiving antiplatelet agents, there was a 10% reduction in preterm birth. No particular subgroup of women in the high-risk group (such as previous severe pre-eclampsia, pre-existing kidney disease, diabetes, chronic hypertension or autoimmune disease) was substantially more or less likely to benefit from antiplatelet agents than any other. There was no statistically significant difference between women who started treatment before 20 weeks (RR 0.87; 95% CI 0.79 to 0.96) and those who started treatment after 20 weeks (RR 0.95; 95% CI 0.85 to 1.06; $P = 0.24$). There were no statistically significant differences between women receiving antiplatelet agents and those receiving placebo in the incidence of potential adverse effects such as antepartum haemorrhage, placental abruption or postpartum haemorrhage, but there was a reduction in risk of preterm birth before 37 weeks (RR 0.93; 95% CI 0.89 to 0.98).

Cost effectiveness

The search strategy retrieved 39 abstracts. Only two papers were ordered;[39;44] of these, one study[44] was excluded because it was not a cost-effectiveness study, leaving one study that met the inclusion criteria, an HTA report.[39] The main focus of the economic analysis was on interventions applied to normotensive women who had no previous history to suggest they were at risk of pre-eclampsia. The results were presented in terms of cost per case of pre-eclampsia avoided. The perspective adopted for the economic evaluation was that of the NHS. Much of the evidence used in the HTA report was from mixed populations and hence the results of the HTA economic analysis were not used by the GDG. The GDG developed an original health economic analysis to assess the cost effectiveness of aspirin compared with no aspirin in women at risk of developing pre-eclampsia (see Appendix H for full details of the analysis).

The estimated total costs for a cohort of 100 women were £270,663 for women receiving aspirin compared with £278,515 for women not taking aspirin, saving £7,852 per 100 women Aspirin generates 0.52 extra QALYs over the duration of the pregnancy. Its cost effectiveness is unequivocal and dominates no aspirin use in women at risk of developing pre-eclampsia The model results were stable in sensitivity analysis: probabilistic sensitivity analysis showed that in 99.9% of the 1000 iterations performed, aspirin remained cost effective.

Evidence statement

Aspirin prophylaxis reduces the occurrence of pre-eclampsia, preterm birth and fetal and neonatal mortality in women at moderate or high risk of developing the condition (high risk being defined as chronic hypertension without superimposed pre-eclampsia or normotension with at least one of previous severe pre-eclampsia, diabetes, chronic hypertension, kidney disease or autoimmune disease, and moderate risk being defined as any other risk factor, in particular first pregnancy, a mild rise in blood pressure and no proteinuria, abnormal uterine artery Doppler velocimetry, positive roll-over test, multiple pregnancy, a family history of pre-eclampsia or being a teenager). One study[42] demonstrated that no particular subgroup of women in the high-risk group was substantially more or less likely to benefit from antiplatelet agents than any other. That study also reported that there was no statistically significant risk of ante- or postpartum maternal haemorrhage, but none of the other studies reported whether or not maternal bleeding had occurred. Two studies included in the Cochrane review followed up children at 12–18 months: one study reported no statistically significant difference in risk of long-term adverse effects at 12–18 months while an unblinded study with high loss to follow up reported a higher risk of fine or gross motor problems with aspirin.

The GDG's economic analysis showed aspirin prophylaxis to be cost saving compared with no aspirin. In high-risk women (those with one or more of previous severe pre-eclampsia, diabetes, chronic hypertension, kidney disease or autoimmune disease) the effect was more marked with, in addition, a reduction in the risk of gestational hypertension. In moderate-risk women (those with risk factors such as being in their first pregnancy, a mild rise in blood pressure with no proteinuria, abnormal uterine artery Doppler velocimetry, positive roll-over test, multiple pregnancy, family history of severe pre-eclampsia or being a teenager) there was a smaller risk

reduction for pre-eclampsia only. There was evidence that the degree of reduction was not dependent on doses of aspirin above 75 mg/day (although the two higher dose groups may have been underpowered to detect a difference owing to the small numbers of studies), and there was no statistically significant difference in effectiveness between treatment before or after 20 weeks. The analysis did not distinguish between risk groups. There was no evidence concerning the use of aspirin in the prevention of pre-eclampsia before 12 weeks.

GDG interpretation of the evidence

The evidence for the use of low-dose aspirin (75 mg/day) is consistent with a small risk reduction for pre-eclampsia and there are sufficient data on the safety of aspirin in the doses used in pre-eclampsia prophylaxis trials to make recommendations for clinical practice. The ratio of benefits (clinical effectiveness) to risks (adverse effects such as maternal ante- or postpartum haemorrhage) is dependent on the risk of developing pre-eclampsia and the numbers needed to treat to prevent pre-eclampsia, with the balance being clearly in favour of advising aspirin prophylaxis for women at high risk of pre-eclampsia and not to those at low risk. The GDG defined high-risk women as those having at least one of the following: previous hypertensive disease during pregnancy, chronic kidney disease, autoimmune disease such as systemic lupus erythematosis (SLE) or antiphospholipid syndrome, type 1 or type 2 diabetes, or chronic hypertension. The GDG's view was that women at moderate risk of pre-eclampsia required an intermediate approach, acknowledging the evidence that aspirin prophylaxis is effective in some such women but that moderate risk factors were poorly defined in the studies, making it difficult to provide objective advice about specific risk factors. The GDG took a cautious approach in formulating recommendations for this group of women, recommending that they be offered aspirin prophylaxis if they had at least two of the following risk factors for pre-eclampsia: first pregnancy, age 40 years or over, pregnancy interval of more than 10 years, family history of pre-eclampsia, BMI 35 kg/m² or more at first visit, or multiple pregnancy. The rationale for this recommendation was that the presence of at least two of these risk factors would confer a greater total risk than any of the factors individually. In some cases, the combined risks would approach those of the factors associated with high risk of pre-eclampsia (for example, BMI greater than 35 kg/m² in nulliparous women[45] and twin pregnancy in nulliparous women).[46]

The GDG also identified the need for further research into the effectiveness of aspirin prophylaxis in women at moderate risk of pre-eclampsia. The dosage relationship was difficult to disentangle. The published systematic review combined studies with aspirin dosages of 60 mg and 75 mg and those using 100 mg and 150 mg to reach a conclusion that higher doses might be more effective, but the GDG's health economic analyses based on the individual doses suggests that 75 mg/day is optimal. This is the lower dose available in the UK (the higher dose being 300 mg/day) and the GDG feels that there is insufficient evidence to justify use of another dose in women regarded as high risk in this guideline. The pathological events that lead to the clinical syndrome of pre-eclampsia begin in the first half of the second trimester of pregnancy and there is a suggestion of a greater effect if aspirin is given before 20 weeks. The GDG believes it is important to start using aspirin from 12 weeks (this being the earliest gestational age for which evidence concerning the use of aspirin in the prevention of pre-eclampsia was identified). There was no conclusive evidence to identify the optimal gestational age at which to discontinue treatment.

Recommendations

Pregnant women should be made aware of the need to seek immediate advice from a healthcare professional if they experience symptoms of pre eclampsia. Symptoms include:

- severe headache
- problems with vision, such as blurring or flashing before the eyes
- severe pain just below the ribs
- vomiting
- sudden swelling of the face, hands or feet.

[This recommendation is adapted from 'Antenatal care' (NICE clinical guideline 62).]

Advise women at high risk of pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Women at high risk are those with any of the following:

- hypertensive disease during a previous pregnancy
- chronic kidney disease
- autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

Advise women with more than one moderate risk factor for pre-eclampsia to take 75 mg of aspirin* daily from 12 weeks until the birth of the baby. Factors indicating moderate risk are:

- first pregnancy
- age 40 years or older
- pregnancy interval of more than 10 years
- body mass index (BMI) of 35 kg/m² or more at first visit
- family history of pre-eclampsia
- multiple pregnancy.

Research recommendation

What is the clinical and cost effectiveness of aspirin prophylaxis for the prevention of pre-eclampsia in women with at least two moderate risk factors?

Why this is important

Although the evidence for the use of low-dose aspirin to reduce the risk of pre-eclampsia in women at high risk is clear, the benefits for those at moderate risk are more difficult to establish and research is required for this group. A problem with the available evidence is the difficulty in quantifying benefit for individual moderate risk factors and determining what interactions exist between them. Although low-dose aspirin appears a safe drug to use in pregnancy there needs to be clearer evidence of benefit within the moderate-risk group of women.

3.3 Other pharmaceutical agents

Clinical effectiveness

Nitric oxide agents (nitric oxide donors – glycerine trinitrate; nitric oxide precursors – L-arginine)

A Cochrane systematic review of six RCTs, involving 310 women, investigated the effectiveness of nitric oxide donors and precursors for preventing pre-eclampsia.[47] [EL = 1+] Studies were included in the review regardless of gestation at trial entry, whether women had normal or high blood pressure or whether women had gestational or chronic hypertension. Women with established pre-eclampsia were excluded. Four studies of good quality in which women developed pre-eclampsia were used ($n = 170$), and two of these also included women who

* In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

developed gestational hypertension. The risk of developing pre-eclampsia was unclear for another two studies, where the quality was also uncertain.

Nitric oxide donors or precursors were compared with either placebo or no intervention. There was no statistically significant effect for (either) nitric oxide donors or precursors with regard to the effects on pre-eclampsia (RR 0.83; 95% CI 0.49 to 1.41).

One study ($n = 46$) evaluated severe pre-eclampsia. No statistically significant difference in the incidence of severe pre-eclampsia between women receiving nitric oxide precursors and those receiving placebo or no treatment was found (RR 0.10; 95% CI 0.01 to 1.87).

Progesterone

A Cochrane systematic review of two RCTs, involving 296 women, evaluated the preventive effect of progesterone on pre-eclampsia.[48] [EL = 1+] Pregnant women with normal or high blood pressure but without proteinuria were included. Women who received any progesterone were compared with women who received placebo or no treatment.

One study ($n = 168$) found no statistically significant difference in the incidence of pregnancy-induced hypertension (RR 0.92; 95% CI 0.42 to 2.01). Another study ($n = 128$) found no statistically significant difference between women who received progesterone and those who received placebo or no treatment in the incidence of pre-eclampsia (RR 0.21; 95% CI 0.03 to 1.77).

Diuretics

A Cochrane systematic review of five studies, involving 1836 women, evaluated the effect of diuretics for preventing pre-eclampsia.[49] [EL = 1+] Four of the included trials involved women at low risk of developing pre-eclampsia, and the fifth involved women at high risk.

Four trials ($n = 1391$) investigated the effect of diuretics compared with placebo or no treatment in the prevention of pre-eclampsia. The occurrence of pre-eclampsia was lower in women receiving diuretics than in women receiving placebo or no treatment but the result was not statistically significant (RR 0.68; 95% CI 0.45 to 1.03). Two studies ($n = 1475$) evaluated new or worsening hypertension and showed similar results: women receiving diuretics had a lower risk of developing new hypertension or a worsening of existing hypertension than women receiving placebo or no treatment but the result was not statistically significant (RR 0.85; 95% CI 0.68 to 1.08).

Low-molecular-weight heparin

An open-label RCT, involving 80 women with the angiotensin-converting enzyme (ACE) DD genotype and a history of pre-eclampsia, investigated the effect of low-molecular-weight heparin (LWMH) on the recurrence rate of pre-eclampsia.[43] [EL = 1−] Forty-one women were randomly assigned to receive dalteparin 5000 international units (IU) per day and 39 women to not receive treatment. Further inclusion criteria were a positive test for at least one of the following: activated protein C resistance, factor V Leiden and factor II 20210A variants, hyperhomocysteinaemia, protein C, protein S, and antithrombin deficiency, anticardiolipin antibodies, and lupus anticoagulant. Women with kidney disease, cardiovascular disease other than hypertension, or pre-existing diabetes were excluded.

Treatment with LMWH (dalteparin 5000 IU/day) was started at the time of a positive pregnancy test. All women received calcium and folic acid supplementation. Women who received LMWH had a lower risk of developing pre-eclampsia than those who did not receive treatment (RR 0.26; 95% CI 0.08 to 0.86). The effect was similar for the development of pre-eclampsia before 34 weeks (RR 0.12; 95% CI 0.02 to 0.91). LMWH showed a 78% reduction in risk for IUGR (RR 0.22; 95% CI 0.08 to 0.61) and an even bigger reduction for IUGR before 34 weeks (RR 0.14; 95% CI 0.03 to 0.56).

Evidence statement

Nitric oxide agents (glycerine trinitrate, L-arginine)

There is limited high-quality evidence on the use of nitric oxide donors in the prevention of hypertensive disease in pregnancy. Existing evidence shows no reduction in hypertensive disorders following use of nitric oxide donors.

Progesterone

There is limited high-quality evidence on the use of progesterone to prevent hypertensive disease during pregnancy. There was no statistically significant reduction in the rate of hypertensive disorders.

Diuretics

There is limited high-quality evidence on the use of diuretics in the prevention of hypertensive disorders of pregnancy in women at risk of these disorders. No benefit in terms of risk reduction for hypertensive disease has been demonstrated.

Low-molecular-weight heparin

One poor-quality RCT provided limited evidence on the effectiveness of LMWH in the prevention of hypertensive disorders during pregnancy. The study showed a clinically and statistically significant reduction in pre-eclampsia and its sequelae in a group of women with previous pre-eclampsia who have demonstrable thrombophilia and who have a specific genotype.

GDG interpretation of the evidence

The available evidence does not suggest a clear benefit to the use of nitric oxide donors in the prevention of hypertensive disorders during pregnancy. There are too few data to comment with any certainty on the use of progesterone to prevent hypertensive disorders of pregnancy, but initial studies do not show promise.

Studies into the value of diuretics in preventing hypertensive disorders during pregnancy were largely carried out in the 1960s and only one study involved high-risk women. The studies did not demonstrate a risk reduction in any setting and diuretics are unlikely to be regarded now as appropriate options for therapy.

The evidence for the use of LMWH, although interesting, is confined to a very specific subgroup of women and the trial used an open-label technique. Some clinicians consider known pre-existing thrombophilia, even without this specific genotype, to be an indication for the use of LMWH, but there is currently insufficient evidence for considering that it may prevent hypertensive disorders during pregnancy. Furthermore, the GDG's view is that there are risks associated with LMWH and so its use has not been recommended.

Recommendation

Do not use the following to prevent hypertensive disorders during pregnancy:

- nitric oxide donors
- progesterone
- diuretics
- low molecular weight heparin.

3.4 Nutritional supplements

Clinical effectiveness

Cochrane systematic reviews were identified for the effects of calcium, antioxidants, marine oils (fish oils or algal oils) and garlic on risk reduction for pre-eclampsia.[50-53] [EL = 1+] A prospective cohort study was also identified in relation to the use of folic acid supplementation.[54] [EL = 2+] Studies in relation to vitamin D supplementation were not sought for this guideline because the importance of vitamin D supplementation in all pregnant women who might have vitamin D deficiency during pregnancy or breastfeeding is highlighted in existing NICE guidance (see 'Antenatal care', NICE clinical guideline 62[1] and 'Maternal and child nutrition', NICE public health guidance 11).[35]

Calcium

A Cochrane systematic review of 12 RCTs, involving 15 206 women, evaluated the effectiveness of calcium in risk reduction for pre-eclampsia.[50] [EL = 1+] Pregnant women at various levels of risk of developing pre-eclampsia were included in the analysis comparing 1.5–2 g calcium carbonate (eight RCTs), elemental calcium from various preparations (three RCTs) and calcium gluconate (one RCT) with placebo or no treatment. A high-risk group included teenagers, women with previous pre-eclampsia, women with increased sensitivity to angiotensin II and women with chronic hypertension. Primiparity alone was not regarded as a high risk factor. All women at a low or average risk of developing hypertensive disorders during pregnancy were considered to be at 'low' risk.

Twelve studies ($n = 15\ 206$) found that women receiving calcium supplementation had an incidence of pre-eclampsia that was half that of women receiving placebo (RR 0.48; 95% CI 0.33 to 0.69). The risk reduction in seven studies ($n = 14\ 619$) involving only low-risk women was 32% (RR 0.68; 95% CI 0.49 to 0.94) whereas the largest reduction in risk (78%) was found across five studies ($n = 587$) involving only high-risk women (RR 0.22; 95% CI 0.12 to 0.42).

The systematic review included only one study that reported severe pre-eclampsia ($n = 8302$) but that study showed no statistically significant effect of calcium supplementation (RR 0.74; 95% CI 0.48 to 1.15). Also, a subgroup analysis showed no statistically significant effect of calcium supplementation on the incidence of pre-eclampsia in women with adequate dietary calcium (RR 0.62; 95% CI 0.32 to 1.20).

Magnesium

No evidence was identified in relation to the effectiveness of magnesium.

Antioxidants

A Cochrane systematic review of ten RCTs, involving 6533 women, evaluated the risk-reduction effects of antioxidants on pre-eclampsia.[51] [EL = 1+] Pregnant women at risk of developing pre-eclampsia were included. Women who received antioxidants were compared with women who received placebo or no antioxidants. Overall, no statistically significant effects were found for antioxidants being effective in risk reduction for pre-eclampsia, severe pre-eclampsia, severe hypertension or preterm birth (before 37 weeks). Nine studies ($n = 5446$) investigated pre-eclampsia (RR 0.73; 95% CI 0.51 to 1.06), two studies ($n = 20\ 495$) investigated severe pre-eclampsia (RR 1.25; 95% CI 0.89 to 1.76), two studies ($n = 4272$) investigated severe hypertension (RR 1.39; 95% CI 0.85 to 2.30) and five studies ($n = 5198$) investigated preterm birth (before 37 weeks) (RR 1.10, 95% CI 0.99 to 1.22). Sensitivity analysis for these outcomes based on trial quality did not change the results.

Subgroup analysis by moderate- and high-risk status for these outcomes showed no statistically significant differences between women receiving antioxidants and the control group. Subgroup analysis by gestational age at entry to the studies for these outcomes did not show any statistically significant differences.

One study ($n = 127$) investigated vitamins C and E combined with aspirin and fish oil and showed a preventive effect on pre-eclampsia (RR 0.07; 95% CI 0.01 to 0.54). Lycopene was investigated in one study ($n = 251$) and it reduced the risk of pre-eclampsia by 52% (RR 0.48; 95% CI 0.14 to 0.97).

No statistically significant effect for the prevention of pre-eclampsia was found for vitamins C and E alone (four studies, $n = 4655$), vitamin C alone (one study, $n = 200$), red palm oil (one study, $n = 113$) or selenium (one study, $n = 100$). Similarly, no statistically significant effect was found for vitamins C and E alone for preventing severe pre-eclampsia (two studies, $n = 2495$).

An RCT from Brazil, including 734 women, investigated the effect of vitamins C and E on the incidence of pre-eclampsia.[55] [EL = 1+] Women were randomised to receive both vitamin C (1000 mg) and vitamin E (400 IU) daily, from the time of enrolment until delivery or diagnosis of pre-eclampsia. Women eligible for enrolment were at 12^{+0} to 19^{+6} weeks and diagnosed with nonproteinuric chronic hypertension or a previous history of pre-eclampsia in their most recent pregnancy. No statistically significant reduction in the rate of pre-eclampsia was found (RR 0.87; 95% CI 0.61 to 1.25).

Folic acid.

A prospective cohort study involving 2951 women evaluated the association between folic acid supplementation early in the second trimester and the risk of developing pre-eclampsia.[54] [EL = 2+] The majority of the women included in the study were white and of high socioeconomic status. Ninety-two percent were taking folic acid supplementation, usually in association with multivitamins containing folic acid at a dose of 1.0 mg or greater. Women who did not take folic acid were more likely to smoke cigarettes during pregnancy and to be younger, multiparous and non-white, with a lower education level and lower household income. Women with twin and higher order pregnancies were excluded. Folic acid in combination with multivitamins showed a 63% reduction in the risk of developing pre-eclampsia (OR 0.37; 95% CI 0.18 to 0.75). Folic acid alone did not show a statistically significant association with pre-eclampsia (RR 0.46; 95% CI 0.16 to 1.31).

Marine oil (fish oils or algal oils)

A Cochrane systematic review of six studies, involving 2755 women, evaluated the effect of marine oil and other prostaglandin precursors on risk reduction for pre-eclampsia.[53] [EL = 1+] Orally administered marine oils (fish oils or algal oils) were compared with placebo or no marine oil. Across five studies ($n = 1831$), women who received marine oil supplementation had the same risk of hypertension without proteinuria as women who did not (RR 1.09; 95% CI 0.90 to 1.33). Similarly, across four studies ($n = 1683$), marine oils did not show a statistically significant effect on the incidence of pre-eclampsia (RR 0.86; 95% CI 0.59 to 1.27). Subgroup analysis by gestational age at trial entry, by singleton or multiple pregnancies, and by risk showed no statistical effect for any of the subgroups.

Garlic

A Cochrane systematic review of one study involving 100 women investigated the effectiveness of garlic for risk reduction for pre-eclampsia.[52] [EL = 1+] Women in their first pregnancy at 28–32 weeks with normal or high blood pressure but no proteinuria were included in the study. They were at moderate risk of pre-eclampsia as determined by a positive roll-over test. Women with established pre-eclampsia were excluded. The included study was of uncertain methodological quality.

The study compared two garlic tablets per day (total 800 mg/day) with placebo. There was no statistically significant difference in the risk of developing pre-eclampsia between the groups (RR 0.78; 95% CI 0.31 to 1.93). Similarly, garlic tablets showed no statistically significant effect for the prevention of gestational hypertension (RR 0.5; 95% CI 0.25 to 1.00).

Evidence statement

Calcium

There is high-quality evidence on the use of calcium supplementation to prevent pre-eclampsia. Where calcium dietary intake is known to be low, calcium supplementation reduces the risk of pre-eclampsia, although the significance of the effect is influenced by pre-eclampsia risk status or diet (and this is associated with trial size in the available evidence – large studies were conducted in women at low-risk, and small trials were conducted in women at high risk). Where calcium intake is known to be adequate, there is no statistically significant reduction in risk. The effect of calcium supplementation is greatest in women at high risk of pre-eclampsia, although the majority of trials in women at risk occurred in low calcium intake groups.

Magnesium

No evidence was identified in relation to the effectiveness of magnesium.

Antioxidants

There is high-quality evidence on antioxidant therapy for the prevention of hypertensive disease during pregnancy. The use of supplementary antioxidants (not in combination with other nutritional supplements) does not reduce the risk of pre-eclampsia or its complications. Subgroup analyses have not identified any high-risk group of women that would benefit from treatment.

Folic acid

There is poor-quality evidence on the use of folic acid in the risk reduction of hypertensive disease during pregnancy although it does suggest a possible benefit. This result is likely to be confounded by other factors and by the use of other vitamins since folic acid supplementation alone did not show a statistically significant effect.

Marine oil (fish oils or algal oils)

There is high-quality evidence examining the effect of marine oil supplementation (using fish oils or algal oils) for the prevention of hypertensive disease during pregnancy. No statistically significant effect was found.

Garlic

There is limited good-quality evidence for the use of garlic in the prevention of pre-eclampsia. No statistically significant effect was found.

GDG interpretation of the evidence

The evidence in relation to calcium is extensive although much of it is in low-risk women, who are outside the scope of this guideline. The benefits are greatest in women with deficient dietary calcium, which is not generally applicable to a UK population. Where high-risk women have been studied, the trials are small and largely confined to deficient dietary calcium populations. Overall, the available evidence is complex and the GDG's view is that a recommendation regarding routine use of additional calcium in women at risk in a UK setting cannot be justified at present. A recommendation for further research in women with risk factors for hypertension in pregnancy who have adequate calcium diets has been formulated by the GDG.

There is no evidence for magnesium supplementation, and poor-quality evidence with multiple confounders for folic acid supplementation alone, in the prevention of hypertensive disorders during pregnancy.

The evidence for garlic is of good quality but limited and shows no reduction in risk.

There is high-quality evidence from large trials and systematic reviews for both marine oil (fish oils or algal oils) and other prostaglandin precursors and for antioxidant supplementation (vitamins C and E). No benefit in terms of prevention of hypertensive disorders was demonstrated.

The GDG's view is that dietary supplementation with folic acid should not be used solely with the aim of preventing hypertensive disorders during pregnancy. However, the GDG notes that the general advice for women who are pregnant or planning to become pregnant to take folic acid up to 12 weeks also applies to women at risk of hypertensive disorders in pregnancy.

Recommendation

Do not recommend the following supplements solely with the aim of preventing hypertensive disorders during pregnancy:

- magnesium
- folic acid
- antioxidants (vitamins C and E)
- fish oils or algal oils
- garlic.

Research recommendation

How clinically and cost effective is calcium supplementation (compared with placebo) for the prevention of pre-eclampsia in women at both moderate and high risk of pre-eclampsia?

Why this is important

Pre-eclampsia and gestational hypertension represents common pregnancy complications. Although large studies on the use of calcium supplementation to prevent hypertensive disorders during pregnancy have been carried out, the variation in populations and calcium status at entry to the studies has made it impossible to reach a conclusion on the value of such treatment in any setting. Calcium supplementation as a treatment is cheap, likely to be well tolerated, and likely to be safe for both the woman and the fetus, although this needs to be confirmed. Even a modest effect would be potentially important given the simplicity of the treatment. A new meta-analysis, using the technique of meta-analysis regression, is needed to clarify the roles of dietary calcium intake and underlying pre-eclampsia risk, taking advantage of subgroup data and seeking additional information from the authors of published trials where possible. Further randomised controlled trials could also be conducted to examine risk reduction in women at moderate and high risk of pre-eclampsia, and to re-examine risk reduction in women at low risk of pre-eclampsia. These trials should consider maternal diet and calcium status and they should evaluate both maternal outcomes (incidence of hypertensive diseases during pregnancy, including severe disease) and neonatal or infant outcomes (neonatal morbidity, infant growth and development).

3.5 Diet

Clinical effectiveness

Advice to restrict dietary salt intake

An RCT involving 361 women evaluated the effect of advice to restrict dietary salt intake during pregnancy for the prevention of pre-eclampsia in women with gestational hypertension.[56] [EL = 1+] Women were eligible for randomisation if they had one or more of the following: two diastolic blood pressure recordings above 85 mmHg, weight gain above 1 kg/week for three successive weeks, or 'excessive' oedema (not defined). Women planning to move to another city and those with conditions associated with an increased risk of pregnancy-induced hypertension (for example, twin pregnancy, diabetes, chronic hypertension or kidney disease) were excluded. The included women were nulliparous and had a diastolic blood pressure below 90 mmHg at their first antenatal visit, which took place before 20 weeks. The study compared advice to reduce dietary salt intake to 50 mmol/day with advice to continue a normal diet. Adherence was tested by checking urinary sodium excretion. Mean sodium excretion after randomisation was 84 mmol/day (target 50 mmol/day) in the low-sodium group and 124 mmol/day in the normal-diet group. Even though the sodium levels were higher than the target, the low-sodium group had a lower sodium level than in the normal diet group. No statistically significant difference was found in the incidence of pre-eclampsia between the women who were advised to have a low-sodium diet and the women who were advised to continue on a normal diet (RR 0.96; 95% CI 0.37 to 2.51).

Energy and protein intake

No evidence was identified in relation to the effectiveness of energy or protein intake.

Evidence statement

Advice to restrict dietary salt intake

There is limited good-quality evidence that advice to adhere to a low-sodium diet does not prevent subsequent development of pre-eclampsia in women with weight gain and mild hypertension.

Energy and protein intake

No evidence was identified in relation to the effectiveness of energy or protein intake.

GDG interpretation of the evidence

There was no clear evidence that advice to restrict dietary salt in women with gestational hypertension prevented pre-eclampsia. However, this does not diminish the importance of an awareness of salt intake in a healthy lifestyle, or of advising dietary salt reduction in chronic hypertension.

Recommendation

Do not recommend salt restriction during pregnancy solely to prevent gestational hypertension or pre-eclampsia.

3.6 Lifestyle

Clinical effectiveness

Rest

A Cochrane systematic review of two RCTs involving 106 women evaluated the effectiveness of rest for reducing the risk of pre-eclampsia in pregnant women with normal blood pressure but a positive roll-over test.[57] [EL = 1+] One study ($n = 32$) investigated advice to rest at home in a left lateral position for 4 hours daily until delivery versus unrestricted activity and found that rest lowered the risk of developing pre-eclampsia (RR 0.05; 95% CI 0.00 to 0.83) but not the risk of developing gestational hypertension (RR 0.25; 95% CI 0.03 to 2.00). The other study ($n = 74$) compared rest plus nutrient supplementation with unrestricted activity plus placebo. The nutritional supplementation consisted of 25 g soya protein, 300 mg calcium and 300 mg linoleic acid three times a week. Advice to rest at home with nutritional supplementation lowered the risk of gestational hypertension (RR 0.15; 95% CI 0.04 to 0.63) and pre-eclampsia (RR 0.13; 95% CI 0.03 to 0.51). However, it is not possible to determine whether the effect was attributable to the advice to rest or to the nutritional supplementation.

Bed rest

No evidence was identified in relation to the effectiveness of bed rest for reducing the risk of hypertensive disorders in pregnancy.

Exercise

A Cochrane systematic review of two RCTs involving a total of 45 women evaluated the effectiveness of moderate-intensity aerobic exercise for the prevention of pre-eclampsia.[58] [EL = 1+] One of the studies ($n = 16$) included women at risk of developing pre-eclampsia because of mild hypertension, a history of hypertensive disorders of pregnancy or a family history of hypertensive disorders of pregnancy. Women with kidney disease, diabetes or multiple pregnancy and those who undertook vigorous exercise with rating of perceived exertion (RPE) > 14 were excluded. The other study ($n = 29$) included pregnant women at less than 34 weeks with gestational diabetes. Women with any other medical or obstetric complications (not further specified), those who were unable to read/write English or those had a current exercise regimen lasting 30 minutes more than twice a week were excluded.

Women undertaking a moderate-intensity exercise regimen were compared with women who did normal physical activity. Two studies ($n = 45$) investigated the effect on pre-eclampsia and found no statistically significant effect (RR 0.31; 95% CI 0.01 to 7.09). One study ($n = 16$) evaluated the effectiveness of exercise on gestational hypertension and no statistically significant effect was found (RR 1.0, 95 CI 0.07 to 13.37).

Maintaining a healthy weight (BMI 18.5–24.9 kg/m²) during pregnancy

No evidence was identified in relation to the effectiveness of maintaining a weight within the healthy range (BMI 18.5–24.9 kg/m², as defined in 'Obesity', NICE clinical guideline 43)[2] during pregnancy. Weight management before, during and after pregnancy is also considered in 'Weight management before, during and after pregnancy' (NICE public health guidance 27).[37]

Working hours and physical activity

A systematic review of five observational studies (two cross-sectional, two cohort studies and one case–control study) evaluated the effect of working hours and physical activity on the incidence of pre-eclampsia.[59] [EL = 2+] The studies were thought to be too different in their outcomes to undertake a meta-analysis.

No studies on the effect of weekly working hours on pre-eclampsia were included. One cross-sectional study on the effect of shift work showed no association between such work and the incidence of pre-eclampsia (RR 1.3; 95% CI 0.8 to 1.9). Two cross-sectional studies assessed the effect of lifting on the incidence of pre-eclampsia. A positive association with lifting heavy loads was found in one study (RR 1.7; 95% CI 1.2 to 2.5) and a negative association with lifting ≥ 13.6 kg versus ≤ 4.5 kg per day in another (RR 0.68; 95% CI 0.47 to 0.98). One cohort study and two cross-sectional studies showed non-statistically significant negative associations with standing (cohort study: RR 0.72; 95% CI 0.32 to 1.59; first cross-sectional study: RR 0.82; 95% CI 0.57 to 1.2; second cross-sectional study: RR 0.7; 95% CI 0.5 to 1.0). Two of the three studies showed no association with physical activities (cohort study: RR 0.7; 95% CI 0.2 to 2.5; cross-sectional study: RR 0.75; 95% CI 0.52 to 1.1). A case–control study showed a positive association with physical activities: moderate or high physical activity at work was associated with a two-fold increase in the odds of severe pre-eclampsia compared with mild activity or no work (RR 2.1; 95% CI 1.18 to 3.75).

Evidence statement

Rest

The evidence for rest in the prevention of hypertensive disorders in pregnancy is limited. A systematic review of two small RCTs showed some potential benefit of rest over unrestricted activity in women with at most a moderate risk of gestational hypertension (normotensive but positive roll-over test).

Bed rest

No evidence was identified in relation to the effectiveness of bed rest for reducing the risk of hypertensive disorders in pregnancy.

Exercise

There was no significant effect of exercise on the reduction of pre-eclampsia.

Weight management during pregnancy

No evidence was identified in relation to the effectiveness of weight management during pregnancy.

Working hours and physical activity

Five studies reviewed the effect of working hours and physical activity but their outcomes were too different for meta-analysis. Another study suggested a slight association with pre-eclampsia and lifting heavy weights but generally poor-quality evidence showed no effect.

GDG interpretation of the evidence

There is insufficient evidence on the use of rest in any form to prevent the onset of hypertensive disease during pregnancy in women at risk of such disease. Although two small RCTs showed some benefit, the results were confounded by the use of nutrient supplements. Similarly, evidence on exercise was too limited to draw any conclusions, although no benefit was seen in two small trials.

The evidence relating to working hours and physical activity is complex and studies differ in quality, definitions and endpoints. No clear association is apparent and the GDG's view is that advice on rest, exercise and work for women at risk of hypertensive disorders during pregnancy should be the same as for healthy pregnant women, as specified in the NICE routine antenatal care guideline.

Recommendation

Advice on rest, exercise and work for women at risk of hypertensive disorders during pregnancy should be the same as for healthy pregnant women (see 'Antenatal care', NICE clinical guideline 62).

4 Management of pregnancy with chronic hypertension

4.1 Introduction

Women with chronic hypertension are at increased risk of pre-eclampsia but even in the absence of this there is increased perinatal mortality. The women frequently have co-morbidities and require care above that offered routinely.

This chapter provides guidance on advice for women with chronic hypertension planning pregnancy, care during pregnancy, use of antihypertensive drugs during pregnancy and the postnatal period, and fetal monitoring in women with chronic hypertension.

4.2 Pre-pregnancy advice

Women with medical disorders should receive advice before pregnancy to ensure their treatment is appropriate and to make them aware of any implications for pregnancy and childbirth. This will include general health issues that all women intending pregnancy should consider (see 'Antenatal care', NICE clinical guideline 62)[1] and additional factors, which for hypertension include both lifestyle factors and safe medication.

4.2.1 Antihypertensive agents

Safety in pregnancy

Evidence was sought on the safety for the fetus of antihypertensive medications used currently for chronic hypertension in non-pregnant women and for those used during pregnancy in this group of women. The safety of antihypertensive drugs is particularly important in the periconceptional period and during the first trimester of pregnancy.

The literature search identified 136 articles, of which ten were retrieved. A further five studies were retrieved having been identified through reference lists in published papers. Of these, five studies were included in this review, four studies for ACE inhibitors and one for angiotensin II receptor blockers (ARBs).

Angiotensin-converting enzyme inhibitors

A retrospective cohort study conducted in the USA investigated the safety of ACE inhibitors in pregnancy.[60] [EL = 2+] All infants enrolled in Tennessee Medicaid and born between 1985 and 2000 were eligible for inclusion. Exclusion criteria were maternal diabetes, exposure to ARBs, exposure to antihypertensive medication beyond the first trimester and exposure to other potential teratogens. The study included 29 096 infants with no exposure to antihypertensive drugs at any time during gestation and 209 infants who were exposed to ACE inhibitors in the first trimester. Eighteen infants had major congenital malformations not related to a chromosomal defect or a clinical genetic syndrome. Infants exposed to ACE inhibitors in the first trimester of pregnancy were more likely to develop congenital malformations compared with infants who were not exposed to any antihypertensive treatment (RR 2.71; 95% CI 1.72 to 4.27).

Another study conducted in the USA[61] [EL = 3] included all adverse outcomes associated with enalapril use in pregnancy that were submitted to the US Food and Drug Administration (FDA) between 1986 and 2000 (108 reports). Adverse pregnancy outcomes were defined as any embryo-fetal adverse outcome, any congenital malformation, IUGR and preterm birth before 37 weeks. Of the 108 cases, 88.9% had embryo-fetal adverse outcomes defined as embryo-fetal

death, miscarriage or stillbirth. In pregnancies that continued past 16 weeks ($n = 95$), 32.5% developed congenital malformations. In pregnancies continuing past 20 weeks ($n = 91$), 50% of the included cases suffered from IUGR and 64.3% were preterm (less than 37 weeks).

A case series of 19 newborns of women exposed to ACE inhibitors was compiled in the USA.[62] [EL = 3] These originated from all women aged 15–44 years enrolled in Tennessee Medicaid who delivered a liveborn or stillborn infant between 1983 and 1988 and who were exposed to ACE inhibitors during pregnancy. Of the 19 infants, two were born preterm with serious life-threatening conditions. One preterm infant had kidney problems requiring dialysis and the other had microcephaly and occipital encephalocele. One infant was born at term but was hypoglycaemic. Sixteen infants were born at term and appeared normal.

A small case series conducted in the UK included 18 women (19 pregnancies) who were exposed to ACE inhibitors during pregnancy[63] [EL = 3] and who were seen at an antenatal hypertension clinic between 1980 and 1997. Seventeen pregnancies ended in a live birth. One woman with type 1 diabetes and one with a mitral valve replacement had early miscarriages (7 and 8 weeks). There were no congenital malformations, kidney dysfunction or neonatal problems reported in infants of women who were exposed to ACE inhibitors at any stage of pregnancy.

Angiotensin II receptor blockers

One systematic review was identified in which ARBs were used in pregnancy.[64] [EL = 3] Because no comparative studies could be identified, case reports, case series and post-marketing surveys were included in this review. In total, 64 published cases of women treated with ARBs during pregnancy were included.

The mean duration of treatment during a pregnancy with an adverse fetal outcome was 26.3 ± 10.5 weeks, compared with 17.3 ± 11.6 weeks for those with a favourable outcome ($P = 0.04$). Of the included cases, 37 women (58%) had favourable and 27 women (42%) had unfavourable outcomes (mainly congenital malformations such as limb, skull, face, kidney and pulmonary defects). Of the women with unfavourable outcomes, ten had been exposed to valsartan, nine to losartan, six to candesartan and two to irbesartan. Of the women with favourable outcomes, six had been exposed to valsartan, one to telmisartan and one to losartan. One study reported 29 cases exposed to candesartan, irbesartan, losartan or valsartan where women gave birth to healthy babies without providing details about how many women were exposed to each drug, its dose, or details about the newborns. More cases of co-morbidities and cigarette smoking were reported among women who had adverse fetal outcomes.

Safety of other antihypertensive medications in pregnancy

Other antihypertensives commonly used in pregnancy are summarised in Table 4.1 (further details are provided in Appendices M and N).

Evidence statement

There are limited good-quality studies on drug safety for ACE inhibitors. One retrospective cohort study of [EL = 2+] and three small case series [EL = 3] were included. The cohort study found congenital malformations to be nearly three times more likely in infants whose mothers took ACE inhibitors compared with those whose mothers did not. Similarly, two small case series found a high prevalence of congenital malformations and IUGR while another small case series found no adverse outcomes.

A systematic review of case reports/series [EL = 3] that investigated the drug safety of ARBs showed that treatment was on average 9 weeks longer in women not taking ARBs compared with those who did. Overall, 42% of pregnancies exposed to ARBs had unfavourable outcomes (defined as any congenital malformation).

Table 4.1 Safety data for antihypertensive drugs in pregnancy

Drug	Route	Safety data
Centrally acting		

Methyldopa	Oral	• Mild hypotension in babies in first 2 days of life • No obvious association with congenital abnormalities
Beta-blockers		
Labetalol	Oral /IV	• No obvious association with congenital abnormalities • Rare mild hypotension in first 24 hours of life • Very rare hypoglycaemia
Atenolol	Oral	• No obvious association with congenital abnormalities • Low birthweight/placental weight • Decreased fetal heart rate described
Metoprolol	Oral	• No obvious association with congenital abnormalities
Oxprenolol	Oral	• No obvious association with congenital abnormalities
Pindolol	Oral	• No obvious association with congenital abnormalities
Alpha-blockers		
Prazosin	Oral	• No obvious association with congenital abnormalities
Calcium-channel blockers		
Nifedipine	Oral	• No obvious association with congenital abnormalities
Amlodipine	Oral	• No reports
Verapamil	Oral/IV	• No obvious association with congenital abnormalities
Diuretics		
Chlorothiazide	Oral	• Possible association with congenital abnormalities • Possible neonatal thrombocytopaenia • Possible neonatal hypoglycaemia/hypovolaemia • Possible maternal/fetal electrolyte imbalances
Bendroflumethiazide	Oral	• No adverse fetal effects • Maternal hypovolaemia
Furosemide	Oral /IV	• No obvious effects
Vasodilators		
Hydralazine	IV	• No obvious association with congenital abnormalities
Diazoxide	IV	• May inhibit uterine contractions • Profound maternal hypotension possible • Neonatal hyperglycaemia reported

GDG interpretation of the evidence

Studies in which ACE inhibitors were used throughout pregnancy suggested increased rates of congenital malformations, IUGR, hypoglycaemia, kidney disease and preterm birth.

Studies of the use of ARBs in pregnancy also showed unfavourable outcomes (mainly congenital malformations).

Despite the relatively poor quality of these studies and the fact that maternal disease severity and other therapeutic drug use could not be excluded as potential causes for the adverse fetal effects reported, there is sufficient concern to avoid the use of ACE inhibitors and ARBs both in women planning pregnancy and for the treatment of hypertension in pregnancy.

For antihypertensive drugs currently in use, other than ACE inhibitors and ARBs, there is no evidence for teratogenicity, although the quality of the data is generally poor. Chlorothiazide may carry the risk of congenital abnormality, neonatal thrombocytopenia, hypoglycaemia and hypovolaemia.

Recommendations

Women with chronic hypertension should be given advice and treatment in line with 'Hypertension: the management of hypertension in adults in primary care' (NICE clinical guideline 34), unless it specifically differs from recommendations in this guideline.

Tell women who take angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs):

- that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy
- to discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

Stop antihypertensive treatment in women taking ACE inhibitors or ARBs if they become pregnant (preferably within 2 working days of notification of pregnancy) and offer alternatives.

Tell women who take chlorothiazide:

- that there may be an increased risk of congenital abnormality and neonatal complications if these drugs are taken during pregnancy
- to discuss other antihypertensive treatment with the healthcare professional responsible for managing their hypertension, if they are planning pregnancy.

Tell women who take antihypertensive treatments other than ACE inhibitors, ARBs or chlorothiazide that the limited evidence available has not shown an increased risk of congenital malformation with such treatments.

4.2.2 Diet

Clinical effectiveness

The evidence for general advice for people with hypertension is contained in 'Hypertension: management of hypertension in adults in primary care' (NICE clinical guideline 34).[3]

GDG interpretation of the evidence

The GDG's view is that pregnant women with chronic hypertension should follow the general advice contained in 'Hypertension: management of hypertension in adults in primary care' (NICE clinical guideline 34)[3] in relation to dietary salt intake.[4] The rationale for this is that chronic hypertension in pregnancy has the same pathogenesis as chronic hypertension in non-pregnant people.

Recommendation

Encourage women with chronic hypertension to keep their dietary sodium intake low, either by reducing or substituting sodium salt, because this can reduce blood pressure. [This recommendation is adapted from 'Hypertension: management of hypertension in adults in primary care' (NICE clinical guideline 34).]

4.3 Prevention of pre-eclampsia

Clinical effectiveness

Aspirin

Section 3.2 presents overall evidence on aspirin for prevention of pre-eclampsia, including a meta-analysis of individual-patient data assessing the effectiveness of antiplatelet agents, mainly aspirin, in preventing pre-eclampsia.[42] [EL = 1++] The study involved a meta-analysis of individual-patient data for women at risk of developing pre-eclampsia, gestational hypertension or IUGR based on their previous pregnancy history, a pre-existing medical condition (for example, kidney disease, diabetes, an immune disorder or chronic hypertension) or obstetric

risk factors early in their current pregnancy (for example, being a primigravida or having a multiple pregnancy). Trials that included women who started treatment postpartum or had a diagnosis of pre-eclampsia at trial entry were excluded, as were studies with quasi-random designs. No language restrictions were applied as selection criteria.

An analysis of all the women at risk of pre-eclampsia showed that antiplatelet agents were effective in reducing the risk (RR 0.90; 95% CI 0.84 to 0.97). While there was no separate analysis for women with chronic hypertension, a subgroup analysis for women with chronic hypertension showed no evidence that effectiveness of antiplatelets differed in women with chronic hypertension and in those with other risk factors but no chronic hypertension ($P = 0.28$).

Dipyridamole

No evidence was identified in relation to the effectiveness of dipyridamole.

Cost effectiveness

Health economic modelling established the cost effectiveness of low-dose aspirin (75 mg/day) for women at risk of pre-eclampsia (see Section 3.2 and Appendix H).

Evidence statement

A meta-analysis of individual-patient data [EL = 1++] that included women with chronic hypertension showed antiplatelet agents to be effective in reducing the risk of developing pre-eclampsia (RR 0.90; 95% CI 0.84 to 0.97). An original health economic analysis also showed aspirin prophylaxis in women at risk of pre-eclampsia to be cost saving.

GDG interpretation of the evidence

The clinical effectiveness evidence relating to antiplatelet agents is best for low-dose aspirin and suggests that treatment modifies the risk of pre-eclampsia in women with chronic hypertension. The time at which treatment should start is unclear but the GDG's view is that it is important to start using aspirin from 12 weeks (this being the earliest gestational age for which evidence concerning the use of aspirin in the prevention of pre-eclampsia was identified). The recommendation to offer aspirin to women with chronic hypertension who are pregnant is covered by the recommendation for all women at high risk of pre-eclampsia that is presented in Section 3.2.

4.4 Treatment of hypertension

This section examines the use of therapies for controlling blood pressure during pregnancy in women with chronic hypertension. This evidence should be considered along with the evidence presented on the treatment of gestational hypertension (see Section 6.4) as some trials of treatment included women with chronic hypertension or gestational hypertension.

4.4.1 Antihypertensives

Clinical effectiveness

Methyldopa

An RCT involving 300 women was conducted in the USA to compare the effect of methyldopa and labetalol with no treatment in chronic hypertension.[65] [EL = 1−] Women with mild or moderate chronic hypertension at 6–13 weeks were randomised to receive methyldopa ($n = 87$), labetalol ($n = 86$) or no treatment ($n = 90$). All included women were seen in the first trimester and were hospitalised at the time of the initial antenatal visit. Women with associated medical complications other than chronic hypertension were excluded. All women were followed up throughout pregnancy. Ninety-one percent of the women had received various antihypertensive treatments before pregnancy, including diuretics, methyldopa and various beta-blocker and other antihypertensive drugs. Methyldopa was started at 750 mg/day and increased as needed to a maximum of 4 g/day to achieve a target systolic blood pressure of less than 140 mmHg and diastolic blood pressure of less than 90 mmHg. Treatment with labetalol started at 300 mg/day and increased to a maximum of 2400 mg/day. If the maximum doses did not

achieve the target blood pressure, hydralazine was added to a maximum oral dose of 300 mg/day. Women in the no-treatment group who had severe hypertension (systolic pressure above 160 mmHg or diastolic blood pressure above 110 mmHg) received methyldopa but remained in the no-treatment group for the analysis. Women receiving methyldopa were as likely as women in the no-treatment group to develop pre-eclampsia (OR 1.21; 95% CI 0.55 to 2.65). Similarly, there were no differences between the treatment group receiving methyldopa and the no-treatment group for the following outcomes: need for additional drugs, incidence of placental abruption, preterm birth (before 37 weeks), SGA and perinatal deaths.

A small RCT ($n = 25$) conducted in the USA investigated the efficacy of methyldopa in chronic hypertension.[66] [EL = 1 –] Inclusion criteria were blood pressure of 140/90 mmHg on two separate occasions separated by at least 6 hours, no evidence of proteinuria (24-hour urine protein below 100 mg), presumed chronic hypertension, gestational age below 34 weeks and singleton pregnancy. Thirteen women received one tablet of methyldopa (250 mg) three times a day and 12 women received a placebo tablet three times a day. These doses were increased every 48 hours as needed to a maximum of two tablets four times a day (2 g) to maintain blood pressure at or below 140/90 mmHg. Pre-eclampsia was defined as a sudden rise in systolic blood pressure by 30 mmHg or in diastolic blood pressure by 15 mmHg, and increased weight gain (more than 2 lbs/week) or proteinuria (2+ or greater on urinary dipstick). The incidence of pre-eclampsia was similar in the two groups (38.4% versus 33.3%) and no statistically significant differences were found for birthweight or ponderal index (both corrected for gestational age).

Labetalol

An RCT investigated the effectiveness of labetalol and methyldopa in chronic hypertension.[65] [EL = 1 –] Women who received labetalol were as likely as women in the no-treatment group to develop superimposed pre-eclampsia (OR 1.06; 95% CI 0.47 to 2.37). There were no differences between the treatment and the no-treatment groups regarding need for additional drugs, the incidence of placental abruption, preterm birth (before 37 weeks), SGA or perinatal deaths.

Atenolol

A UK RCT evaluated the effectiveness of atenolol in women with chronic hypertension.[67] [EL = 1 –] Women were recruited at between 12 and 24 weeks if they had a systolic blood pressure between 140 and 170 mmHg or diastolic blood pressure between 90 and 110 mmHg on two occasions separated by at least 24 hours. Women who had any contraindications to the use of a beta-blocker were excluded. Of a total of 33 women, 15 were randomised to receive atenolol, 14 to receive placebo and four were withdrawn from the study. Women in the treatment group received 50 mg/day atenolol, increasing until blood pressure was below 140/90 mmHg or a dose of 200 mg/day was reached.

There was a statistically significant difference between the treatment and placebo groups in mean diastolic blood pressure (difference 7.0 mmHg; 95% CI 2.9 to 10.0; $P = 0.001$) and in mean birthweight (difference 901 g; 95% CI 440 to 1380; $P < 0.001$). However, there was no statistically significant difference between the treatment and placebo groups in mean systolic blood pressure after entry to the study (that is, after treatment; $P = 0.08$)). Babies born to mothers who received atenolol were on average 901 g lighter (mean birthweight 2629 g) than babies born to women receiving placebo (mean birthweight 3530 g).

Calcium-channel blockers

No evidence was identified in relation to nifedipine, amlodipine or nicardipine.

Diuretics

An RCT conducted in the USA investigated the effectiveness of continuing diuretics or stopping diuretics during pregnancy.[68] [EL = 1 –] The study population consisted of 20 women who had a documented history of long-term hypertension and were receiving diuretics at entry to the study. Women were randomly assigned to continue their diuretic throughout pregnancy ($n = 10$) or to discontinue immediately ($n = 10$). All women included had mild or moderate hypertension (diastolic blood pressure between 90 and 110 mmHg) and were in the first trimester of pregnancy. To keep systolic blood pressure below 160 mmHg and/or diastolic blood pressure below 110 mmHg, methyldopa was added when necessary. All women were prescribed a daily

diet containing approximately 2 g of sodium and they were instructed to avoid the addition of salt during food preparation. There was no statistically significant difference between the groups in the incidence of pre-eclampsia (treatment group: 1/10; stopping treatment: 1/10; $P > 0.05$), nor for any of the other outcomes investigated (birthweight, SGA, 5-minute Apgar score).

Antihypertensives with diuretics

An RCT from the USA evaluated the effectiveness of antihypertensive treatment on pregnancy outcome in women with mild chronic hypertension.[69] [EL = 1−] Inclusion criteria were a documented history of hypertension (blood pressure at or above 140/90 mmHg) before pregnancy or the finding of hypertension on at least two consecutive measurements more than 24 hours apart before 20 weeks, as well as classification of the hypertension as mild by severity criteria, including a diastolic blood pressure below 100 mmHg and the absence of target-organ damage. Nulliparous women, women whose pregnancies were complicated by other major medical problems such as diabetes or multiple pregnancy, and women whose antenatal care began after 20 weeks were excluded. Study participants were randomly allocated to treatment ($n = 29$) or no-treatment groups ($n = 29$). Eleven women in the treatment group received methyldopa and thiazide, ten continued to use hydralazine and thiazide, and eight continued with methyldopa, hydralazine and thiazide. No placebo was used for the no-treatment group. Women in the no-treatment group whose hypertension became aggravated received antihypertensive treatment before giving birth but remained in the no-treatment group in the analysis. The intervention was continued antihypertensive treatment. Four women (of 29) in the treatment group had pregnancy-aggravated hypertension (defined as increase in diastolic blood pressure to a level above 100 mmHg on two consecutive measurements 6 hours or more apart) compared with 13 women (of 29) in the no-treatment group ($P < 0.05$). None of the other outcomes investigated (preterm birth before 37 weeks, birthweight below 2501 g, fetal distress or SGA) showed statistically significant differences between the two groups.

Evidence statement

There were limited good-quality trials to evaluate the effectiveness of alpha- and beta-blockers and methyldopa for treatment of chronic hypertension during pregnancy. Results from two trials showed no difference between women receiving methyldopa or labetalol and those receiving placebo in the incidence of pre-eclampsia. A third trial found atenolol to be useful in lowering diastolic blood pressure but not systolic blood pressure.

Only one trial of small sample size [EL = 1−] was found using diuretics alone. The results showed no statistically significant differences between the two study groups for any outcomes of interest.

One RCT [EL = 1−] compared continued treatment with discontinued treatment with antihypertensive agents and diuretics in women with mild chronic hypertension. It was found that women on antihypertensive treatment had a lower incidence of pregnancy-aggravated hypertension than women on no treatment. The groups were similar regarding all other outcomes.

4.4.2 Level of blood pressure control

Clinical effectiveness

One RCT[70] [EL = 1+] conducted in Egypt compared effectiveness of applying 'tight' versus 'less tight' control of mild chronic or gestational hypertension in pregnancy. Women with blood pressure of 140–159/90–99 mmHg with live fetus(es) and gestational age 20–33^{+6} weeks were included. Women with blood pressure equal to or higher than 160/100 mmHg, proteinuria, diabetes, chronic kidney disease or fetal anomalies were excluded. Women were randomly assigned to tight blood pressure target ($n = 63$; target blood pressure less than 130/80 mmHg) or less tight blood pressure target ($n = 62$; target blood pressure 130–139/80–89 mmHg). There were no statistically significant differences in baseline characteristics between the two groups.

Women in the tight control group were less likely to develop severe hypertension (RR 0.32; 95% CI 0.14 to 0.74) and to be admitted to hospital (RR 0.39; 95% CI 0.18 to 0.86). Babies born to women in the tight group had higher gestational ages at delivery (36.6 ± 2.2 weeks

versus 35.8 ± 2.2 weeks; $P < 0.05$) and were less likely to born preterm (RR 0.52; 95% CI 0.28 to 0.99). There were no statistically significant differences between groups in terms of intrauterine fetal death, admission to NICU or IUGR.

One multicentre RCT[71] [EL = 1+] (a pilot trial for the Control of Hypertension in Pregnancy Study; CHIPS) was conducted in Canada, New Zealand, Australia and the UK to compare the effects of tight and very tight control of blood pressure in women with chronic or gestational hypertension (diastolic blood pressure 90–109 mmHg, live fetus(es) and 20–33^{+6} weeks). The study excluded women with diastolic blood pressure consistently lower than 85 mmHg, severe systolic hypertension (170 mmHg or higher), proteinuria, contraindication to less tight or tight control, contraindication to pregnancy prolongation, or delivery anticipated within a week, or known lethal or major fetal anomaly. Women were randomly assigned to either 'less tight' ($n = 66$; target diastolic blood pressure 100 mmHg) or 'tight' ($n = 66$; target diastolic blood pressure 85 mmHg) control of blood pressure. There were no significant differences in baseline characteristics between the two groups.

No statistically significant differences were found between the two groups in terms of gestational age at delivery (36.9 ± 3.0 weeks versus 36.3 ± 3.3 weeks; $P = 0.278$), serious perinatal complications (14% versus 22%; RR 0.63; 95% CI 0.29 to 1.36), care in NICU (23% versus 34%; RR 0.67; 95% CI 0.38 to 1.18), serious maternal complications (4.6% versus 3.1%; RR 1.48; 95% CI 0.26 to 8.55) or the number of women who received magnesium sulphate for pre-eclampsia (15% versus 19%; RR 0.82; 95% CI 0.38 to 1.77). No differences were found in the proportions of infants less than 10th centile for gestation (30% versus 29%; RR 1.04; 95% CI 0.61 to 1.76) or in infants with birthweight less than 2500 g (35% versus 49%; RR 0.71; 95% CI 0.47 to 1.07). Pre-eclampsia was reported in 62% of the 'less tight' group and in 52% of the 'tight' group (RR 1.34; 95% CI 0.94 to 1.89), and severe hypertension in 58% versus 40% (RR 1.42; 95% CI 1.00 to 2.01).

One meta-regression conducted in Canada included 45 RCTs with a total of 3773 women taking antihypertensives (including methyldopa, acebutolol, atenolol, labetalol, metoprolol, oxprenolol, pindolol, propranolol, bendroflumethiazide, chlorothiazide, hydrochlorothiazide, ketanserin, hydralazine, isradipine, nicardipine, nifedipine, verapamil and clonidine).[72] [EL = 1+] The aim of the study was to estimate the association of treatment-induced mean arterial pressure with SGA babies and birthweight. A greater difference in MAP between control and treatment groups was associated with a higher proportion of SGA babies (15 RCTs, 1587 women; $P < 0.05$). In relation to birthweight, when one RCT was excluded owing to outlying results, a 10 mmHg fall in mean arterial pressure was associated with a 145 g decrease in birthweight (26 RCTs, number of women not reported; $P < 0.05$). However, three RCTs reported statistically significant differences in gestational age at delivery between the two groups. There was no statistically significant association between mean arterial pressure and birthweight when the RCT with outlier results was included (27 RCTs, 2305 women; P value not reported).

Evidence statement

One RCT [EL = 1+] investigated 'tight' versus 'less tight' control of hypertension in women with chronic or gestational hypertension. Women in the tight control group were less likely to develop severe hypertension or to be admitted to hospital and their babies were less likely to be born preterm. There were no differences in intrauterine fetal death, admission to NICU or IUGR.

Another RCT [EL = 1+] looked at 'tight' versus 'less tight' control of hypertension in women with existing or gestational hypertension. There were no significant differences between the groups in terms of gestational age at delivery, serious perinatal complications, care in NICU, serious maternal complications or the number of women who received magnesium sulphate for pre-eclampsia. However, the risk of severe hypertension was lower in women in the tight control group.

A meta-regression [EL = 1+] showed that every 10 mmHg fall in mean arterial pressure in women taking antihypertensives (including methyldopa, acebutolol, atenolol, labetalol, metoprolol, oxprenolol, pindolol, propranolol, bendrofluazide, chlorothiazide, hydrochlorothiazide, ketanserin, hydralazine, isradipine, nicardipine, nifedipine, verapamil and clonidine) was associated with a 145 g decrease in birthweight.

4.4.3 Bed rest

Clinical effectiveness

An RCT was conducted in Zimbabwe on the effectiveness of hospital admission for bed rest compared with continued normal activities at home.[73] [EL = 1+] Two hundred and eighteen women with singleton pregnancies and blood pressure of 140/90 mmHg or higher, without proteinuria and at between 28 and 38 weeks of gestation were included in the study; of these, 33 had chronic hypertension. Women who were symptomatic, had a diastolic blood pressure of 100 mmHg or higher, a caesarean section scar or an antepartum haemorrhage during the pregnancy were excluded. Women were randomly allocated to hospital bed rest ($n = 15$ with chronic hypertension) or encouraged to continue normal activities at home ($n = 18$ with chronic hypertension). No statistically significant differences were found for development of severe hypertension, proteinuria or severe proteinuria.

Evidence statement

One small RCT from Zimbabwe showed no difference in the incidence of pre-eclampsia between women with chronic hypertension who had bed rest in hospital and those did not.

GDG interpretation of the evidence

Antihypertensives

The evidence from trials on treatment of blood pressure does not make it possible to determine the preferred antihypertensive agent for pregnant women with chronic hypertension. The available evidence suggests that antihypertensive treatment reduces the risk of severe hypertension but not the development of proteinuria. The GDG's view is that further research is needed in relation to the efficacy and safety of antihypertensive agents when used during pregnancy by women with chronic hypertension. Such research should include placebo-controlled trials as well as head-to-head comparisons between various antihypertensive agents.

Level of blood pressure control

The GDG considered that the effect on fetal growth with some agents (mainly beta-blockers) is related to their greater effectiveness in reducing blood pressure. Two good-quality studies looking at the effect of 'tight' blood pressure control (defined differently in each trial) showed an increased risk of severe hypertension with less tight control of blood pressure, but no other differences in maternal or perinatal outcomes, including fetal growth. A meta-regression of RCTs demonstrated that the more blood pressure was reduced in women taking antihypertensives (including (including methyldopa, acebutolol, atenolol, labetalol, metoprolol, oxprenolol, pindolol, propranolol, bendroflumethiazide, chlorothiazide, hydrochlorothiazide, ketanserin, hydralazine, isradipine, nicardipine, nifedipine, verapamil and clonidine), the more the birthweight of their babies was reduced.

The GDG's view is that treatment should aim to lower blood pressure from the moderate or severe range while avoiding excessive reductions that may affect fetal growth, whatever antihypertensive agent is used. Women with evidence of target-organ damage from hypertension will need a lower target blood pressure than women without these changes, in line with 'Hypertension', NICE clinical guideline 34,[3] which includes the following recommendations:

> Drug therapy reduces the risk of cardiovascular disease and death. Offer drug therapy to:
> - patients with persistent high blood pressure of 160/100 mmHg or more
> - patients at raised cardiovascular risk (10-year risk of cardiovascular disease ≥20% or existing cardiovascular disease or target-organ damage) with persistent blood pressure of more than 140/90 mmHg).

Bed rest

The evidence in relation to bed rest comes from a small RCT that examined the effectiveness of hospital bed rest and showing no beneficial effect of such rest in women with chronic hypertension. Prolonged bed rest can increase the risk of venous thromboembolism and the GDG advises against such rest.

Secondary chronic hypertension

The GDG's view is that pregnant women with secondary chronic hypertension should be offered referral to a specialist in hypertensive disorders, such as an obstetric physician, a renal physician, an endocrinologist or a specialist in connective tissue disease.

Recommendations

In pregnant women with uncomplicated chronic hypertension aim to keep blood pressure less than 150/100 mmHg.

Do not offer pregnant women with uncomplicated chronic hypertension treatment to lower diastolic blood pressure below 80 mmHg.

Offer pregnant women with target-organ damage secondary to chronic hypertension (for example, kidney disease) treatment with the aim of keeping blood pressure lower than 140/90 mmHg.

Offer pregnant women with secondary chronic hypertension referral to a specialist in hypertensive disorders.

Offer women with chronic hypertension antihypertensive treatment dependent on pre-existing treatment, side-effect profiles and teratogenicity.

Research recommendation

Which antihypertensive agent is best for use in women with chronic hypertension during pregnancy?

Why this is important

The literature on anti-hypertensive medication in women with chronic hypertension is inadequate to determine if any particular agent would offer advantages over placebo control or other antihypertensive agents. All drugs in common use have potential side effects and potential fetal and neonatal effects. As chronic hypertension is becoming more common it seems sensible to revisit therapy to ensure both efficacy and safety. Randomised controlled trials should be carried out in women with chronic hypertension during pregnancy to assess the commonly used antihypertensive agents relative to placebo control, and to compare different antihypertensives using head-to-head trials. Outcomes of interest are: level of blood pressure control for each type of drug, incidence of pre-eclampsia and complications of severe hypertension, efficacy, side effects, and perinatal morbidity and mortality.

4.5 Fetal monitoring

Clinical effectiveness

The fetus in a pregnancy complicated by hypertension may be at risk of increased perinatal mortality and morbidity. There were no specific studies dealing with fetal monitoring in pregnancies complicated by chronic hypertension. However, guidance on monitoring can be extrapolated from the overall data presented in Chapter 8. This is reasonable because the central problem for all pregnancies complicated by any form of hypertension is placental insufficiency with a common path of effect, which is IUGR, fetal hypoxia and ultimately fetal death.

Uterine artery Doppler velocimetry

Uterine artery Doppler velocimetry has been proposed as a method of pregnancy assessment that may, if abnormal, indicate an increased risk of pre-eclampsia. A search was carried out for studies that, as far as possible, included chronic hypertension, and five studies were identified

One diagnostic study[74] [EL = II] studied women with chronic hypertension ($n = 42$). Thirty-seven women had mild hypertension (blood pressure 140–159/90–109 mmHg) and five had severe hypertension (blood pressure above 160/110 mmHg). Women with autoimmune disorders treated

with corticosteroids and those with fetal chromosomal abnormalities or rhesus isoimmunisation were excluded. All women underwent uterine Doppler velocimetry at 23–24 weeks.

Using resistance index to interpret Doppler velocimetry results (abnormal being above the 90th percentile of the reference group) showed a sensitivity of 78% and specificity of 45% for pre-eclampsia superimposed on chronic hypertension. When the endpoint was IUGR, the test showed a sensitivity of 50% and a specificity of 39%.

Another diagnostic study[75] [EL = II] examined a group of 78 pregnant women with chronic hypertension (diastolic blood pressure above 90 mmHg). Uterine artery Doppler velocimetry was conducted at 24–25 weeks and the endpoint outcomes were pregnancy-aggravated hypertension (diastolic blood pressure increase of more than 15 mmHg), superimposed pre-eclampsia, IUGR or placental abruption. When used for any complication, the resistance index (abnormal being 2 SD above normal for gestational age) had a sensitivity of 76% and specificity of 84%. Using bilateral notch and abnormal resistance index had a sensitivity of 62% and specificity of 100%.

Three diagnostic studies[76-78] [EL = II] investigated the use of uterine artery Doppler velocimetry at 22–24 weeks of gestation in women with high-risk pregnancy (previous pre-eclampsia, previous stillbirth, previous placental abruption, previous IUGR, chronic hypertension, diabetes, autoimmune disease, kidney disease or habitual abortion).

Using resistance index gave a sensitivity of 78–97% and a specificity of 42–71% for prediction of pre-eclampsia. One study[78] ($n = 116$) reported data on the use of resistance index in predicting IUGR, with a sensitivity of 84% and specificity of 39% for SGA babies.

The evidence is summarised in Tables 4.2 and 4.3.

Evidence statement

One diagnostic study [EL = II] showed that uterine artery Doppler velocimetry at 24 weeks has a sensitivity of 78% and specificity of 45% when using resistance index to identify risk of pre-eclampsia.

Studies where women with chronic hypertension were included as part of a larger group of high-risk women showed sensitivities of 80% and over but poor specificity (generally less than 70%).

GDG interpretation of the evidence

No studies have evaluated fetal monitoring specifically in women with chronic hypertension and therefore inference on monitoring must be made from general studies of high-risk pregnancies that included women with chronic hypertension.

Fetal monitoring

In spite of the lack of relevant evidence for the use of biometry in hypertensive disorders, the GDG felt that the recognised risk of IUGR in this group results in a need for fetal biometry and fetal monitoring within its recommendations.

Uterine artery Doppler velocimetry

The information on the predictive value of uterine artery Doppler velocimetry in women at high risk of pre-eclampsia, including those with chronic hypertension, is of poor quality and uses a variety of Doppler measurements and outcomes.

Overall, the GDG's view is that the negative predictive ability and the sensitivity are not sufficiently discriminatory to allow clinicians to alter management for individual women. Given that women with chronic hypertension are already advised to take aspirin during pregnancy, the GDG has not found any evidence that discrimination by Doppler velocimetry would drive clinical intervention or alter outcomes.

Recommendations relating to fetal monitoring for women with chronic hypertension are presented in Chapter 8.

Table 4.2 Use of uterine artery Doppler velocimetry to predict pre-eclampsia or IUGR in women with chronic hypertension or mixed high-risk factors

Study	Population demographic characteristics	Gestational age	Index	Parameter	Pre-eclampsia	IUGR	Notes
Caruso *et al.* (1996), Italy[74]	$n = 42$ chronic hypertension: 37 mild (blood pressure 140–159/90–109 mmHg), 5 severe (blood pressure > 160/110 mmHg) Mean age 32 years (range 23–44 years)	23–24 weeks	RI: abnormal > 90th percentile Reference group: 1084 healthy pregnant women	For high-risk women: Sensitivity: Specificity: PPV: NPV	 78% 45% 28% 88%	 50% 39% 8% 88%	Exclusion criteria: autoimmune disease, fetal chromosomal abnormalities, Rhesus isoimmunisation Antihypertensive therapy was discontinued and restarted if blood pressure exceeded 160/110 mmHg. Endpoint: superimposed pre-eclampsia
Parretti *et al.* (2003), Italy[76]	$n = 144$, previous pre-eclampsia ($n = 87$), previous stillbirth ($n = 22$), previous placental abruption ($n = 11$), previous IUGR ($n = 24$) Median age 34.5 years (range 27–41 years), gravidity 2 or 3, parity 1 or 2	24 weeks	RI: abnormal ≥ 0.58	Sensitivity: Specificity: PPV: NPV:	77.8% 67.6% 44.4% 90.1%	Not reported	Exclusion criteria: smoking, kidney disease, cardiovascular disease, diabetes, multiple pregnancy, fetal chromosomal abnormalities, or if already on low-dose aspirin Pre-eclampsia = blood pressure > 140/90 mmHg, proteinuria > 300 mg/24 hours Endpoint: pre-eclampsia
Caforio *et al.* (1999), Italy[77]	$n = 335$, chronic hypertension ($n = 89$), pre-eclampsia ($n = 76$), type 1 diabetes ($n = 58$), autoimmune disease ($n = 53$), systemic lupus erythematosus ($n = 17$), kidney disease ($n = 34$), previous stillbirth ($n = 91$), IUGR ($n = 20$) and recurrent miscarriage ($n = 119$) Mean age 31 ± 4.8 years	$n = 249$ at 22–24 weeks	RI: abnormal > 90th percentile	Sensitivity: Specificity: PPV: NPV:	97% 71% 31% 99%	77% 72% 37% 94% (endpoint: birthweight < 1750 g)	Exclusion criteria: congenital defects, chromosomal abnormalities, multiple gestations, infections, Rhesus isoimmunisation, non-immune hydrops, prelabour rupture of the membranes, intrauterine deaths or delivery before 26 weeks of gestation. Endpoint: pre-eclampsia
Coleman *et al.* (2000), New Zealand[78]	$n = 116$, chronic hypertension ($n = 69$), previous recurrent pre-eclampsia ($n = 24$), previous early-onset pre-eclampsia requiring delivery at or before 32 weeks ($n = 25$), previous placental abruption ($n = 10$), kidney disease ($n = 40$), systemic lupus erythematosus ($n = 13$), antiphospholipid syndrome ($n = 5$) Mean age 31 years (range 19–43 years), 31/116 were nulliparous and 18% smoked during pregnancy	22–24 weeks	RI: any abnormal > 0.58 Bilateral notch	Sensitivity: Specificity: PPV: NPV: Sensitivity: Specificity: PPV: NPV	91% 42% 37% 92% 29% 86% 47% 74%	84% 39% 33% 87% 36% 89% 53% 79%	Exclusion criteria: multiple pregnancies and pregnancies with recognised fetal abnormalities Endpoint: pre-eclampsia Data for both RI > 0.58, any notch, and any RI and any notch were also reported

NPV = negative predictive value; PPV = positive predictive value; RI = resistance index

Table 4.3 Use of uterine artery Doppler velocimetry to predict pregnancy-aggravated hypertension, superimposed pre-eclampsia, IUGR and placental abruption in women with chronic hypertension

Study	Population demographic characteristics	Gestational age	Index	Parameter	Pre-eclampsia	Notes
Frusca *et al.* (1998), Italy[75]	*n* = 78 chronic hypertension (diastolic blood pressure > 90 mmHg, no proteinuria)	24–25 weeks	RI: abnormal = > 2SD above normal mean for gestational age	Sensitivity: Specificity: PPV: NPV:	76% 84% 64% 91%	Exclusion criteria: multiple pregnancy, fetal structural or chromosomal abnormalities Pre-pregnancy antihypertensives were stopped at first visit (7–10 weeks), restarted if diastolic blood pressure exceeded 100 mmHg. All women took 50 mg/day aspirin from 12 weeks Endpoints: pregnancy aggravated hypertension (diastolic blood pressure increase of more than 15 mmHg), superimposed pre-eclampsia, IUGR and placental abruption

NPV = negative predictive value; PPV = positive predictive value; RI = resistance index

4.6 Antenatal consultations

The frequency of antenatal contacts for women with chronic hypertension cannot be specified as the care of each pregnancy needs to be individualised. The only evidence on antenatal schedules is found in 'Antenatal care', NICE clinical guideline 62[1] and the GDG is clear that the routine schedule alone would be inadequate for pregnant women with chronic hypertension. If proteinuria develops then the care would become that of a woman with pre-eclampsia (see Chapter 7).

Recommendation

In women with chronic hypertension, schedule additional antenatal consultations based on the individual needs of the woman and her baby.

4.7 Timing of birth

Clinical effectiveness

Maternal indications

No specific evidence was identified in relation to timing of birth for women with chronic hypertension. The GDG considered that the advice on timing of birth for women with chronic hypertension should be the same as for women with gestational hypertension (see Section 6.7). If proteinuria develops then the management becomes that described for women with pre-eclampsia (see Section 7.7).

Fetal indications/

No specific evidence was identified for fetal monitoring in pregnancies complicated by chronic hypertension. Because women with chronic hypertension are more likely to have underlying vascular disease than women with gestational hypertension, and possibly those with pre-eclampsia, the risk of IUGR is probably greater. Decisions about the timing of birth in women with chronic hypertension is, therefore, more likely to involve consideration of fetal indications, such as poor growth or impending fetal death.

GDG interpretation of the evidence

The GDG's view is that timing of birth in women with chronic hypertension should be the same as for women with gestational hypertension. However, fetal indications for IUGR and impending fetal death may occur more commonly in women with chronic hypertension.

Recommendations

Do not offer birth to women with chronic hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment, before 37 weeks.

For women with chronic hypertension whose blood pressure is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician.

Offer birth to women with refractory severe chronic hypertension, after a course of corticosteroids (if required) has been completed.

4.8 Postnatal investigation, monitoring and treatment

This section relates to women with chronic hypertension who have not developed pre-eclampsia.

Frequency of postnatal observations or investigations

No evidence was identified in relation to frequency of observations or investigations.

Choice of antihypertensive treatment

No evidence was identified in relation to choice of antihypertensive treatment in the postnatal period for women with chronic hypertension. The use of antihypertensive drugs during breastfeeding is discussed in Chapter 11.

GDG interpretation of the evidence

There is little evidence to support the use of basic observations in the postnatal period and these should be largely clinically driven in type and frequency. Peak blood pressure in the postnatal period occurs 3–5 days after the birth and blood pressure should be assessed at this time, whatever the birth or postnatal setting. Similarly, blood pressure monitoring would be sensible if treatment were altered, in this case by restarting previous antihypertensive therapy. The GDG's view is that women with chronic hypertension should be offered a formal medical review at the postnatal review (6–8 weeks after the birth) and that their pre-pregnancy care team should conduct the review. The review should include measurement of blood pressure, urine testing and review of antihypertensive drugs.

Target blood pressures will be those used in long-term treatment of hypertension.

There is no evidence in relation to the effectiveness of antihypertensive drugs in the postnatal period for women with chronic hypertension. The GDG's view is, therefore, that antenatal antihypertensive treatment should continue in the postnatal period.

The GDG is aware of a Medicines and Healthcare products Regulatory Agency (MHRA) newsletter (May 2009 issue of the MHRA *Drug Safety Update*, available at www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON046451) that identifies methyldopa as the antihypertensive of choice during pregnancy and breastfeeding. However, the MHRA *Drug Safety Update* does not reflect the well-recognised association between methyldopa and clinical depression. Although maternal depression was reported in only one of the 21 studies considered by the GDG in relation to methyldopa,[79] the GDG's view is that this drug should not be used in the postnatal period because women are already at risk of depression at this time; use of methyldopa should be stopped within 2 days of the birth where feasible.

Recommendations

In women with chronic hypertension who have given birth, measure blood pressure:

- daily for the first 2 days after birth
- at least once between day 3 and day 5 after birth
- as clinically indicated if antihypertensive treatment is changed after birth.

In women with chronic hypertension who have given birth, aim to keep blood pressure lower than 140/90 mmHg.

In women with chronic hypertension who have given birth:

- continue antenatal antihypertensive treatment
- review long-term antihypertensive treatment 2 weeks after the birth.

If a woman has taken methyldopa† to treat chronic hypertension during pregnancy, stop within 2 days of birth and restart the antihypertensive treatment the woman was taking before she planned the pregnancy.

Offer women with chronic hypertension a medical review at the postnatal review (6–8 weeks after the birth) with the pre-pregnancy care team.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

5 Assessment of proteinuria in hypertensive disorders of pregnancy

5.1 Introduction

The reliable detection of significant proteinuria is most important in women with new-onset hypertension during pregnancy because it distinguishes between those pregnancies with pre-eclampsia and those with gestational hypertension and this sets the scene for future monitoring and management. Significant proteinuria is defined internationally as the urinary excretion of more than 300 mg protein in a 24-hour period, and this is included in definitions of pre-eclampsia. Traditionally proteinuria has been assessed by dipstick (which can be read visually or by an automated device) and confirmed by a 24 hour urine collection. However, the use of spot urinary protein : creatinine ratio and spot urinary albumin : creatinine ratio to estimate proteinuria is well established in the management of chronic kidney disease. More recently they have started to be used in the management of hypertensive disorders of pregnancy.

This section reviews the evidence on testing for proteinuria.

5.2 Measurement of proteinuria

5.2.1 Visual and automated reading of dipsticks

Clinical effectiveness

Visual reading of protein dipsticks

One systematic review[80] [EL = Ia] investigated the value of point-of-care dipstick (reagent-strip) urinalysis in the prediction of significant proteinuria. Seven diagnostic test studies were included ($n = 1841$ women). Studies using convenience sampling or in which blinding was not used were excluded. No language restrictions were reported. Populations included pregnant women without complications, pregnant women with hypertension and women with pregnancies complicated by kidney disease. Six studies looked at visual reading of dipsticks and two looked at automated reagent-strip reading devices. The reference standard cut-off point for significant proteinuria was taken as 300 mg/24 hours or 300 mg/litre in a 24-hour urine collection. When 300 mg/24 hours was not used as the definition for significant proteinuria, these studies were not included in the systematic review. None of the studies included in the systematic review stated whether the completeness of 24-hour urine collection was validated (for example, by creatinine concentration or volume).

At a reference standard cut-off point of 300 mg/24 hours, with proteinuria of 1+ on a visually read dipstick (six studies, $n = 1738$), sensitivities of 55% (95% CI 37% to 72%, $n = 680$) and specificities of 84% (95% CI 57% to 95%, $n = 1058$) were reported. A PPV of 72% (95% CI 53% to 86%), an NPV of 30% (95% CI 23% to 40%) and statistically significant LRs were also found (LR+ 3.48; 95% CI 1.66 to 7.27, LR− 0.6; 95% CI 0.45 to 0.8). There was significant heterogeneity across all studies ($P < 0.001$). Univariate subgroup analysis stratified for items of study did not provide an explanation for the observed variation in diagnostic performance.

A well-conducted prospective study carried out in the UK included 171 pregnant women at 20 weeks or later and with new-onset hypertension.[81] [EL = Ib] All women had a systolic blood

pressure greater than 140 mmHg or a diastolic blood pressure greater than 90 mmHg. The visual dipstick test was performed on an early-morning urine sample collected on the second morning of the 24-hour collection, and compared with quantitative protein excretion obtained from the 24-hour sample. Whether or not the completeness of the collection was validated was not reported. Sensitivity, specificity and positive and negative LRs were 51% (95% CI 39% to 62%), 78% (95% CI 68% to 86%), 2.27 (95% CI 1.47 to 3.51) and 0.64 (95% CI 0.49 to 0.82), respectively.

Another well-conducted prospective study carried out in South Africa investigated 198 pregnant women who presented with hypertension at 28–34 weeks.[82] [EL = Ib] The study included women with gestational hypertension as well as those with pre-eclampsia. Routine visual dipstick urinanalysis was performed by a midwife before a 24-hour urine sample was collected over the next day. It was not reported whether the first-morning void of urine was used in the analysis, nor whether the researchers validated the completeness of the 24-hour urine collection. The sensitivity, specificity and positive and negative LRs for 1+ proteinuria or more were 51% (95% CI 39% to 63%), 84% (95% CI 76% to 90%), 3.23 and 0.58, respectively.

Automated reading of protein and microalbumin dipsticks

The systematic review that looked at visual reading of protein dipsticks (reagent strips)[80] [EL = Ia] also reported two studies that investigated the use of automated reagent-strip reading devices. At a reference standard cut-off point of 300 mg/24 hours, with proteinuria of 1+ on an automated reagent-strip reading device (one study, $n = 171$, details of automated reagent-strip reading device not reported), a sensitivity of 82% ($n = 77$) and a specificity of 81% ($n = 94$) were reported. A PPV of 77.7%, an NPV of 15.6% and statistically significant LRs were also reported (LR+ 4.27; 95% CI 2.78 to 6.56, LR− 0.22; 95% CI 0.14 to 0.36). The other study included in the systematic review[83] was not considered for the guideline review because it used a cut-off point of 300mg/l.

A prospective diagnostic study[81] conducted in the UK and published after the systematic review [EL = Ib] looked at visual and automated reading of protein and microalbumin dipsticks (reagent strips). The visually read protein dipstick (Multistix® 8SG) had a sensitivity of 51% (95% CI 39% to 62%), whereas the automated reading device (Multistix® 8SG read using a Clinitek® 50 urine chemistry analyser) had a sensitivity of 82% (95% CI 71% to 90%). The specificity for the visually read protein dipstick was 78% (95% CI 68% to 86%) and for the automated reading was 81% (95% CI 71% to 88%). The diagnostic accuracy (measured by the area under the receiver operating characteristic (ROC) curve) was 0.67 (95% CI 0.59 to 0.75) for the visually read protein dipstick and 0.84 (95% CI 0.79 to 0.90) for the automated reagent-strip reading device. Using a threshold of 3.4 mg/mmol for albumin:creatinine ratio, visually read microalbumin dipsticks (Microalbustix™), had a sensitivity of 49% (95% CI 38% to 61%), a specificity of 83% (95% CI 74% to 90%) and a diagnostic accuracy of 0.67 (95% CI 0.60 to 0.74). An automated reagent-strip reading device (Clinitek® microalbumin dipsticks, the dipstick version of the Microalbustix™ for automated reading, read using the Clinitek® 50 urine chemistry analyser) had a sensitivity of 58% (95% CI 47% to 70%), a specificity of 83% (95% CI 74% to 90%) and a diagnostic accuracy of 0.72 (95% CI 0.65 to 0.79).

Cost effectiveness

The economic literature search identified no published economic evaluations examining the cost effectiveness of automated urinalysis compared with routine visual urinalysis in the quantification of proteinuria in pregnant women with mild or moderate gestational hypertension. Using published clinical data, the GDG developed an original health economic model to inform the guideline recommendations. The results of these models are summarised below and further details are provided in Appendices K and L.

In order to compare the cost effectiveness of automated and visual urinalysis we first considered which test threshold to use for the detection and diagnosis of pre-eclampsia. There is uncertainty about whether 1+ represents the optimal threshold for a positive test result;[80] using a higher threshold increases the PPV and reduces the number of 24-hour urine collections undertaken and the associated cost. However, it also results in more missed cases, which can lead to unnecessary maternal and neonatal mortality and morbidity. As the threshold is increased from 1+ to 2+, the sensitivity of the test decreases while specificity increases. In other words, false

negatives (undiagnosed cases of pre eclampsia) increase while false positives (cases wrongly diagnosed as pre-eclampsia) fall. The question for this guideline is whether the cost associated with setting the threshold at 1+ (that is, the cost of more 24-hour urine collections) is offset by identifying more women with pre-eclampsia and avoiding the mortality, morbidity and costs associated with undiagnosed pre-eclampsia.

We conducted separate analyses for 1+ versus 2+ thresholds for visually read dipsticks and automated reagent-strip reading devices. The analysis showed that a threshold of 1+ was cost effective when compared with 2+ for both visual urinalysis and automated urinalysis. The estimated incremental cost-effectiveness ratios (ICERs) for 1+ versus 2+ threshold for visual urinalaysis was estimated to be £10,767 per QALY while that of automated urinalysis was estimated to be £8,650 per QALY. There were no data for protein:creatinine ratio comparing different thresholds and therefore the cost-effectiveness of protein:creatinine ratio at different thresholds was not evaluated.

Having established the cost-effective threshold, we compared automated urinalysis with visual urinalysis using a 1+ threshold. The base-case analysis showed that, overall, use of automated urinalysis was the less expensive strategy compared with visual urinalysis for a cohort of 60 000 women with moderate hypertension. Automated urinalysis is £51,540 cheaper and generates 415 extra QALYs. As automated urinalysis is less costly and more effective, it is said to dominate visual urinalysis. For women with mild hypertension, the model showed that, overall, automated urinalysis was a more expensive strategy than visual urinalysis although it generates more health benefits. The incremental cost of automated urinalysis (compared with visual urinalysis) was £23,430 and the incremental QALY gain was 415, giving an ICER of £57/QALY. Using a threshold of £20,000 per QALY, automated urinalysis is cost effective when compared with visual urinalysis.

Evidence statement

One systematic review[80] [EL = Ia] investigated the value of point-of-care reagent-strip (dipstick) urinalysis in the prediction of significant proteinuria, as shown in Table 5.1.

Table 5.1 Summary of results from the systematic review of urinalysis dipstick techniques by Waugh *et al.*[80]

Reference cut -off	Type of dipstick reading	Proteinuria level	Predictive results	
300 mg/24 hours	Visual (6 studies, *n* = 1738)	≥ 1+	Sensitivity	55%
			Specificity	84%
			PPV	72%
			NPV	30%
			LR+	3.48 (95% CI 1.66 to 7.27)
			LR–	0.60 (95% CI 0.45 to 0.80)
	Automated (1 study, *n* = 171)	≥ 1+	Sensitivity	82%
			Specificity	81%
			PPV	77.7%
			NPV	15.6%
			LR+	4.27 (95% CI 2.78 to 6.56)
			LR–	0.22 (95% CI 0.14 to 0.36)

LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value

A prospective diagnostic study [EL = Ib] showed that 1+ proteinuria on a visually read dipstick had a sensitivity, specificity and positive and negative LRs of 51% (95% CI 39% to 63%), 84% (95% CI 76% to 90%), 3.23 and 0.58, respectively.

A prospective diagnostic study [EL = Ib] compared visual reading of protein and microalbumin dipsticks and use of automated reagent-strip reading devices. The visually read protein dipstick had a sensitivity of 51% (95% CI 39% to 62%), a specificity of 78% (95% CI 68% to 86%), and

a diagnostic accuracy of 0.67 (95% CI 0.59 to 0.75), whereas the automated reading device had a sensitivity of 82% (95% CI 71% to 90%), a specificity of 81% (95% CI 71% to 88%), and diagnostic accuracy 0.84 (95% CI 0.79 to 0.90). Using a threshold of 3.4 mg/mmol for the albumin : creatinine ratio, the visually read microalbumin dipstick showed a sensitivity of 49% (95% CI 38% to 61%), a specificity of 83% (95% CI 74% to 90%) and a diagnostic accuracy of 0.67 (95% CI 0.60 to 0.74). The automated reagent-strip reading device, however, showed a sensitivity of 58% (95% CI 47% to 70%), a specificity of 83% (95% CI 74% to 90%) and a diagnostic accuracy of 0.72 (95% CI 0.65 to 0.79).

The GDG's health economic analysis showed that the 1+ threshold was cost effective when compared with a 2+ threshold for visual urinalysis (£10,767/QALY) and automated urinalysis (£8,650/QALY). A further health economic analysis showed that automated urinalysis was cost saving compared with visual urinalysis for quantification of proteinuria in women with gestational hypertension. This analysis was based on diagnostic accuracy data for a single commercially available automated reagent-strip reading device.

5.2.2 Duration of urine collection

Clinical effectiveness

Three studies evaluated the diagnostic value of urine protein assessed by 2-hour, 4-hour and 12-hour urine collections, respectively.[84-86] One study [EL = II] was conducted in Thailand,[85] one [EL = III] was conducted in the USA[86] and one [EL = II] was conducted in Nigeria.[84] The study conducted in Thailand excluded samples where urinary protein concentration was < 15 mg/kg over the 24-hour collection. The other studies did not report whether the completeness of urine collection was validated.

A prospective study conducted in Thailand, including 164 pregnant women diagnosed as having a hypertensive disorder in pregnancy, investigated the diagnostic accuracy of the first 4-hour urinary protein : creatinine ratio.[85] [EL = II] Women included in this study had either a resting blood pressure of 140/90 mmHg or higher after 20 weeks, or chronic hypertension before 20 weeks with new-onset proteinuria. Women with kidney disease, liver disease, urinary tract infection or chronic hypertension with prior proteinuria were excluded. Fifty-two women had gestational hypertension and 112 had pre-eclampsia. None of the included women had superimposed pre-eclampsia. Urine was collected in separate containers, starting with a 4-hour collection directly followed by a 20-hour urine collection. The first void morning urine of the first day of the collection was excluded. The total 24-hour urine protein and creatinine was calculated by summation of the first 4-hour and the consecutive 20-hour urine protein and creatinine. The best cut-off point for 4-hour protein : creatinine ratio to predict significant proteinuria (defined as 300 mg protein or more in a 24-hour urine collection) determined by an ROC curve was 33.9 mg/mmol. Sensitivity was 81% and specificity 88% (no CIs were reported). At this cut-off point, the positive and negative LRs derived from the reported sensitivity and specificity were 6.75 and 0.22, respectively.

A study conducted in the USA investigated the diagnostic accuracy of total urine protein measured in a 12-hour urine collection compared with total protein measured in a 24-hour collection.[86] [EL = III] The study involved 29 pregnant women admitted to a medical centre for evaluation of possible pre-eclampsia and/or characterisation of severity of the pre-eclampsia. Women included in the study were not confined to bed rest. Twenty-five women had pre-eclampsia, of whom two had mild pre-eclampsia, 16 had severe pre-eclampsia, and seven had superimposed pre-eclampsia. Of the remaining four participants, two had isolated chronic hypertension and two had hypertension that did not meet the criteria for chronic hypertension or pre-eclampsia. Two consecutive 12-hour urine samples were collected and the total protein determined in the first 12-hour sample and in the combined 24-hour sample. The sample collection was initiated without regard to the time of the day. Significant protein in the 12-hour sample was taken as total protein above 150 mg. Sensitivity was 96% and specificity 100%. CIs were not calculated because one cell contained the value zero.

A prospective diagnostic study[84] [EL = II] conducted in Nigeria compared urine protein from 2-hour and 12-hour samples with 24-hour samples for diagnosing pre-eclampsia. The study included 86 women (gestational age at least 20 weeks) who had provided 24-hour urine

samples for protein and creatinine clearance as requested by their physicians to rule out pre-eclampsia. Women with chronic hypertension, chronic kidney disease, pathological vaginal discharge or urinary tract infection, and those that had vulva or vaginal cleansing with antiseptics or skin cleansers were excluded. Urine was collected from women at 9 a.m. on the day after admission, then 2 hours later, 12 hours later and 24 hours later. The first three samples (9 a.m. on the day after admission, then 2 hours later and 12 hours later) were compared with the 24-hour protein sample in detecting significant proteinuria. In comparison with the gold standard test (24-hour urine collection), the visually read dipstick was found to have a sensitivity of 81% and a specificity of 47% (PPV 59%; NPV 71%). The 2-hour protein had a sensitivity of 86% and a specificity of 82% (PPV 77%; NPV 89%) while the 12-hour protein had a sensitivity of 89% and a specificity of 93% (PPV 84%; NPV 92%).

Evidence statement

One study [EL = II] compared the diagnostic accuracy of proteinuria detected in a 4-hour urine collection with that of a 24-hour urine collection. At the optimal threshold of 0.30, the sensitivity was 81% and specificity 88% and the positive LR was 6.75 and the negative LR 0.22.

Another small study [EL = III] compared the diagnostic value of protein measured in a 12-hour urine collection with a 24-hour urine collection. The study population included had a wide range of hypertensive disorders. This study reported high sensitivity (96%) and specificity (100%). However, the small sample size should be taken into account when interpreting these results.

One prospective diagnostic study [EL = II] showed that in, comparison with 24-hour urine collection, urine protein from 2-hour and 12-hour collections had sensitivities of 86% and 89%, specificities of 82% and 93%, PPVs of 77% and 84%, and NPVs of 89%, and 92%, respectively. The visually read dipstick had a sensitivity of 81% and a specificity of 47% (PPV 59%; NPV 71%).

5.2.3 Use of microalbumin in the assessment of proteinuria

Clinical effectiveness

One well-conducted UK study[81] [EL = Ib] evaluated the diagnostic value of visual reading of a microalbumin dipstick and an Italian study[87] [EL = III] examined the diagnostic value of 24-hour urine microalbumin excretion measured in a 24-hour sample.

The prospective diagnostic study conducted in the UK[81] [EL = Ib] included 171 women at 20 weeks or more and with new-onset hypertension. All women had a sustained systolic blood pressure of greater than 140 mmHg or a diastolic blood pressure of greater than 90 mmHg. Women with chronic hypertension were excluded. Visual reading of a microalbumin dipstick was performed on an early-morning sample of urine collected on the second morning of the 24-hour collection, and compared with quantitative protein excretion of more than 300 mg/24 hours. The threshold value chosen for the albumin:creatinine ratio was 3.4 mg/mmol and the sensitivity, specificity and positive and negative LRs were 49% (95% CI 38% to 61%), 83% (95% CI 74% to 90%), 2.9 (95% CI 1.76 to 4.78) and 0.61 (95% CI 0.48 to 0.78), respectively.

The Italian study investigated the diagnostic accuracy of the albumin excretion rate, and included 108 pregnant hypertensive women of whom 40 (37%) had chronic hypertension.[87] [EL = III] The included women were at 28–30 weeks and had proteinuria below 300 mg/24 hours at the time of sampling. No exclusion criteria were stated. The timing of the tests, whether outcome assessors were blinded to the results, and whether first morning voids were excluded, was not reported. The 24-hour microalbumin excretion was compared with 24-hour urine protein excretion. The threshold for the albumin excretion rate of 49 mg/litre was determined by the value of the mean + 2 SD. The study reported a sensitivity of 70% (95% CI 39.7% to 89.2%), a specificity of 98.9% (95% CI 94.0% to 99.9%), and positive and negative LRs of 63.0 (95% CI 8.60 to 461.28) and 0.30 (95% CI 0.12 to 0.78), respectively.

Evidence statement

One study [EL = Ib] found visual reading of a microalbumin dipstick to have a sensitivity of 49% and a specificity of 83%. A study with a lower evidence level [EL = III] found 24-hour microalbumin to have a sensitivity of 70% and a specificity of 99%.

5.2.4 Use of protein:creatinine ratio and albumin:creatinine ratio in the assessment of proteinuria

Clinical effectiveness

One systematic review[88] [EL = Ib] assessed the accuracy of spot protein:creatinine ratio and spot albumin:creatinine ratio compared with 24-hour urinary collection for the detection of significant proteinuria in hypertensive pregnant women. The review included diagnostic studies in women with gestational hypertension (five studies, $n = 423$), pre-eclampsia or suspected pre-eclampsia (five studies, $n = 523$) or any hypertensive disorder of pregnancy (three studies, $n = 268$). Ten of the studies were prospective and 11 were cross-sectional. Individual study quality ranged from 7 to 12 on the quality assessment of studies of diagnostic accuracy in systematic reviews (QUADAS) tool.[89] Case–control studies were excluded, as was one study that was not in English or French. The review authors contacted the authors of the original publications for more data where necessary.

Towards the end of this guideline's development, the GDG identified two further studies that examined the relationship between spot protein:creatinine ratio and 24-hour urinary protein in women with hypertensive disorders during pregnancy.[90;91] [EL = II] Both studies validated the completeness of the 24-hour urine collection, and the GDG's view was that they were sufficiently important to be included in the guideline review.

Spot protein:creatinine ratio

Thirteen studies included in the published systematic review[88] ($n = 1214$) looked at spot protein:creatinine ratio. No consistency was found with how cut-off points were reported and eight different cut-off points were used (median 24 mg/mmol; range 17–57 mg/mmol). Only three of the protein:creatinine ratio studies included in the review validated the completeness of the 24-hour urinary collection using a measure of total creatinine concentration or urinary volume.

The first of the three studies was conducted in Brazil (n = 47 women).[92] [El = II] It included women with arterial hypertension who were referred by an antenatal clinic or obstetric emergency service. Women with multiple pregnancy, premature rupture of the membranes, secondary hypertension and impaired kidney function were excluded. Twenty-four hour urine collection had to contain more than 800 mg of creatinine to be considered an adequate or complete collection. Diagnostic accuracy statistics were not reported clearly. A sensitivity and PPV were reported for a cut-off point of 90.4 mg/mmol, but the specificity and NPV were not reported for this cut-off point. It was possible to determine from an ROC curve that a cut-off point of 57 mg/mmol gave a sensitivity and specificity of approximately 95%, but exact figures were not reported. The systematic review authors reported the following diagnostic accuracy statistics for a cut-off point of 30 mg/mmol: sensitivity 94%, specificity 80%, LR+ 4.7 and LR– 0.08.

The second of the three studies was conducted in the USA (n = 126 women).[93] [EL = II] Women with new-onset persistent hypertension, worsening hypertension or proteinuria were included, while women with bacteriuria and those who had bed rest for longer than 24 hours were excluded. The systematic review authors contacted the authors of the original study to confirm that the 24-hour urine collection was validated. Adequate collection was defined as a urinary creatinine of greater than 1 g/day and urine volume greater than 1 litre/day. The optimal cut-off point for detecting 300 mg of protein in 24 hours was 23.7 mg/mmol, with an area under the ROC curve of 0.86. It was possible to determine from the ROC curve that a cut-off point of 23.7 mg/mmol gave a sensivity of approximately 90% and a specificity of approximately 75%, but exact figures were not reported. The systematic review authors reported the following diagnostic accuracy statistics for a cut-off point of 23.7 mg/mmol: sensitivity 86.8%, specificity 100%, LR+ 3.88 and LR– 0.17.

The last of the three studies included in the systematic review was conducted in Turkey (n = 185 women) and was the only study that reported diagnostic accuracy statistics for a specified protein:creatinine ratio cut-off point.[94] [EL = II] The study included women with new-onset mild hypertension and excluded those with a coexisting urinary tract infection, pre-existing kidney disease and chronic hypertension. Samples with an inadequate collection (< 10 mg of creatinine per kg of body weight in 24 hours) were also excluded. With a cut-off point of 22.6 mg/mmol, the sensitivity was 80%, specificity 74%, PPV 45%, NPV 93%, LR+ 3.08 and LR− 0.27.

The first of the additional studies identified by the GDG was conducted in the USA (n = 116 samples from 95 women).[90] [EL = II] Women with an incomplete collection (total creatinine < 1000 mg for non-obese women, < 850 mg for obese women, or < 13 mg/kg body weight) were excluded from the study. With a protein:creatinine ratio cut-off point of 31.6 mg/mmol, the sensitivity was 66%, specificity 95%, PPV 93% and NPV 75%.

The second of the additional studies identified by the GDG was conducted in Mexico (n = 927 women admitted to a hypertensive diseases of pregnancy clinic with or without suspected pre-eclampsia).[91] [EL = II] Women with co-existing urinary tract infection, membrane rupture or inadequate 24-hour urine collection (20% more or less creatinine than the level predicted by the Cockroft–Gault equation) were excluded. With a protein:creatinine ratio of 33.9 mg/mmol, the sensitivity was 98%, specificity 99%, PPV 97%, NPV 99%, LR+ 79.2 and LR− 0.02.

A meta-analysis was conducted for the guideline using the findings from the three studies that clearly reported diagnostic accuracy data and validated 24-hour urine protein collection using a total creatinine value (one study from the published systematic review and the two additional studies identified by the GDG).[90;91;94] However, there was significant heterogeneity between the three studies (I^2 > 96% on all pooled statistics) and so pooling of results was considered to be inappropriate.

Spot albumin:creatinine ratio

Two studies (n = 225) looked at spot albumin:creatinine ratio (both considered good quality by use of the QUADAS tool). With a cut-off point of 2 mg/mmol, the spot albumin:creatinine ratio had a sensitivity of 94%, a specificity of 94%, a positive LR of 15.7 and a negative LR of 0.05 compared with 24-hour proteinuria. With a cut-off point of 27 mg/mmol, the spot albumin:creatinine ratio had a sensitivity of 95%, a specificity of 100%, a positive LR of infinity and a negative LR of 0.05 compared with 24-hour albuminuria. Neither of the studies stated whether the completeness of the 24-hour urine collection had been validated. For this reason, health economic evaluation of the spot albumin:creatinine ratio was not undertaken.

Cost effectiveness

An original health economic model was developed to compare the following screening strategies for proteinuria in women with mild or moderate gestational hypertension:

- use of protein:creatinine ratio alone
- use of an automated reagent-strip reading device followed by protein:creatinine ratio in women with a positive test result on the automated reagent-strip reading device
- use of an automated reagent-strip reading device followed by a validated 24-hour urine collection in women with a positive test result on the automated reagent-strip reading device.

The model is described in detail in Appendix M. The model inputs included published estimates of sensitivity and specificity from the five studies that compared protein:creatinine ratio with validated 24-hour urine collection.[90-94] The largest study suggested that the strategy of using protein:creatinine ratio alone was cost effective for women with mild or moderate hypertension (it dominated the other strategies).[91] Using protein:creatinine ratio test characteristics based on the other four studies, an automated reagent-strip reading device followed by 24-hour urine collection was most cost effective and sometimes dominant.[90;92-94] The cost effectiveness was highly influenced by test sensitivity, which drives the QALY gain in the model. The strategy of using an automated reagent-strip reading device followed by protein:creatinine ratio was not cost effective because it was dominated by the use of protein:creatinine ratio alone when protein:creatinine ratio sensitivity was assumed to be high and dominated by the use of the

automated reagent-strip reading device followed by 24-hour urine collection when sensitivity was assumed to be relatively low, primarily because false negatives accrue at each stage of a sequential testing strategy.

Evidence statement

Five studies evaluated the diagnostic accuracy of spot protein:creatinine ratio compared with validated complete 24-hour urine collection for the detection of significant proteinuria in hypertensive pregnant women.[85;90-94] [EL = II] The diagnostic accuracy statistics for the individual studies are summarised in Table 5.2. Diagnostic accuracy statistics were not reported clearly in the two remaining original publications, but a published systematic review[89] reported results calculated after contacting the authors of the original publications, and these results are also summarised in Table 5.2. When the results of the five studies were meta-analysed, statistically significant heterogeneity was identified. The slightly different cut-off values used in the various studies could have been a contributing factor. Heterogeneity could also have arisen because of differences in laboratory methods used to estimate protein and creatinine. None of the studies was undertaken in the UK. Two studies were undertaken in the USA,[93;90] where the clinical setting may have been similar to the UK, and provided some indication of what to expect in the UK, but even these studies had widely different sensitivities (66% and 89%).

A health economic analysis suggested that the cost effectiveness of the various strategies for measuring urinary protein was sensitive to differences in the diagnostic accuracy statistics (particularly the sensitivities) of protein:creatinine ratio and the automated reagent-strip reading device, with a strategy of using protein:creatinine ratio only being preferred when the sensitivity of the test was very high, and a strategy of using the automated reagent-strip reading device followed by 24-hour urine collection being preferred at lower sensitivities of the protein:creatinine ratio test. The strategy of using the automated reagent-strip reading device followed by protein:creatinine ratio was not cost effective because it was dominated by the use of protein:creatinine ratio alone or the automated reagent-strip reading device followed by 24-hour urine collection, depending on the model value of protein:creatinine ratio sensitivity.

Table 5.2 Summary of results of studies that reported spot protein:creatinine ratio for proteinuria and validated the results of 24-hour urine collection

Study	Study characteristics	Results
Al *et al.* (2004), Turkey[94]	Cut-off point: 22.6 mg/mmol 185 samples	Sensitivity: 80% (95% CI 64% to 91%) Specificity: 74% (95% CI 66% to 81%) PPV: 45% NPV: 93%
Dwyer *et al.* (2008), USA[90]	Cut-off point: 31.6 mg/mmol) 116 samples	Sensitivity: 66% (95% CI 52% to 78%) Specificity: 95% (95% CI 86% to 99%) PPV: 93% NPV: 75% LR+: 13.21 (95% CI 4.3 to 40.5)
Leanos-Miranda *et al.* (2007), Mexico[91]	Cut-off point: 33.9 mg/mmol 927 samples	Sensitivity: 98% (95% CI 96% to 99%) Specificity: 99% (95% CI 98% to 99.5%) PPV: 97% (95% CI 95% to 99%) NPV: 99 %(95% CI 98% to 100%) LR+: 79.2 (95% CI 39.8 to 157.7) LR−: 0.02 (95% CI 0.01 to 0.04)
Ramos *et al.* (1999), Brazil[92] using data reported by Cote *et al.* (2008)[88]	Cut-off point: 30 mg/mmol 47 samples	Sensitivity: 94% Specificity: 80% LR+: 4.7 LR−: 0.08
Wheeler *et al.* (2007), USA[93] using data reported by Cote *et al.* (2008)[88]	Cut-off point: 23.7 mg/mmol 126 samples	Sensitivity: 86.8% Specificity: 77.6% LR+: 3.88 LR−: 0.17

CI = confidence interval; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value

One systematic review[88] [EL = Ib] compared the accuracy of spot albumin:creatinine ratio compared with 24-hour urine collection (for protein or albumin) for the detection of significant proteinuria in hypertensive pregnant women. With a cut-off point of 2 mg/mmol, the diagnostic accuracy statistics for a comparison with 24-hour proteinuria were: sensitivity 94%, specificity 94%, LR+ 15.7 and LR– 0.05. With a cut-off point of 27 mg/mmol, the statistics for comparison with 24-hour albuminuria were: sensitivity 95%, specificity 100%, LR+ infinite and LR– 0.05.

GDG interpretation of the evidence

The GDG recognised the considerable variations that existed in the study populations, designs and quality. None of the studies considered the relationship of proteinuria to clinical outcomes.

Visual reading of urinary reagent strips (dipsticks) is a poor test for the diagnosis of pre-eclampsia and a protein-negative result on dipstick testing does not exclude significant proteinuria (above 300 mg/24 hours). Higher thresholds of dipstick testing have higher specificity and higher positive LRs but, at a cut-off of 1+, visual reading of dipsticks has a sensitivity of 55% and a specificity of 84%. The use of an automated reagent-strip reading device improves test performance, with a sensitivity of 82% and specificity of 81% using a 1+ threshold, and appears to be cost saving. The GDG noted, however, that the evidence of cost effectiveness of the automated reagent-strip reading device was based on a single commercially available device, although there are others on the market. The comparison of visual and automated urinalysis led the GDG to conclude that visual reading of reagent strips should not be used in the secondary care setting (in contrast to routine antenatal care where visual reading is recommended practice).

Standardisation of the protein:creatinine ratio to 30 mg/mmol showed a test performance virtually identical to that of the automated reagent-strip reading device (sensitivity 83.6% and specificity 76.3%), even though most studies did not validate the completeness of the 24-hour urine collection. However, the standardisation carried out was not precisely to a value of 30 mg/mmol for each study, but to the cut-off point closest to this. A cut-off point of 30 mg/mmol has, to some extent, been selected only because it was thought to correlate to 300 mg/24 hours, rather than determining optimal cut-off points using robust statistical methods.

When only those studies that validated the completeness of 24-hour urine collection were considered (a total of five studies), there was evidence that a threshold of approximately 30 mg/mmol had very high test accuracy for prediction of 24-hour urine protein above 300 mg. Although the available evidence was not extensive, it appeared that the time of day at which the spot protein:creatinine ratio was taken was not important.

The GDG acknowledges that the evidence base for such a critical diagnostic test is not as scientifically robust as they would wish, and that thresholds for all testing strategies relate to biological variation in protein excretion and not to serious maternal or perinatal outcomes.

For the initial diagnostic test in secondary care (generally in an obstetric day unit), there is a balance to be struck between the convenience to the woman and healthcare professionals of point-of-care testing using an automated reagent-strip reading device (which, if the test result were negative, would allow early discharge of the woman) and a laboratory test that would provide accurate quantification of proteinuria (spot protein:creatinine ratio). At present, spot protein:creatinine ratio results would take a few hours to be made available (the GDG estimates 2–4 hours), although the woman would not need to be admitted to hospital to await the results. Various service models exist and the choice of initial test strategy might depend on this. The GDG's view is, therefore, that both of these tests are suitable for estimating proteinuria in a secondary care setting in women with new-onset hypertension to help distinguish gestational hypertension from pre-eclampsia. There is insufficient high-quality evidence to consider using the spot albumin:creatinine ratio in clinical practice at present.

Quantification of proteinuria should follow diagnosis. Where the protein:creatinine ratio has been used for diagnosis, the results obtained can be used directly for quantification, with 30 mg/mmol being the most pragmatic cut-off point to define significant proteinuria. Where an

automated reagent-strip reading device has been used, then either a spot protein:creatinine ratio or 24-hour urinary protein can be used (with the usual threshold of 300 mg for 24-hour urine collection and the requirement of hospital admission). An economic model suggested that the most cost-effective screening strategy was driven largely by the test sensitivity. Depending on the test sensitivity (and there was significant heterogeneity between studies that provided estimates of sensitivity for spot protein:creatinine ratio), the strategies of using spot protein:creatinine ratio alone or using an automated reagent-strip reading device followed by 24-hour urine collection could be considered to be cost effective. However, the strategy of using an automated reagent-strip reading device followed by protein:creatinine ratio was not cost effective because it was dominated by the use of protein:creatinine ratio alone. If the protein:creatinine ratio has high sensitivity and specificity, then using protein:creatinine ratio alone for diagnosis and quantification is the most cost-effective option. If, however, the sensitivity and specificity are not as good then the use of an automated reagent-strip reading device followed by 24-hour urine collection tends to be more cost effective than using protein:creatinine ratio sequentially (because the false negative rate of a sequential diagnostic pathway accumulates multiplicatively).

In formulating their recommendations, the GDG considered the practicalities of the three different strategies. The use of an automated reagent-strip reading device has the potential to allow women whose test results are negative to return home quickly. The use of a spot protein:creatinine ratio might be preferred to 24-hour urine collection for quantification of proteinuria after screening based on automated urinalysis for similar reasons (since the results of spot protein:creatinine testing would be available within 2–4 hours). Thus the convenience to women suspected of having pre-eclampsia (and to their healthcare professionals) could influence the choice of screening strategy.

The GDG therefore decided to recommend spot protein:creatinine testing as an option for quantification of proteinuria after screening based on automated urinalysis, even though the strategy of using spot protein:creatinine ratio alone would be preferable on purely economic grounds. Another factor that might influence the choice between the recommended screening strategies is the availability of spot protein:creatinine testing in local laboratories.

The GDG noted the importance of formal validation of the completeness of 24-hour urine collection. Where this method of quantifying proteinuria is to be used, the GDG recommends that completeness should be evaluated formally. Comparison of total creatinine estimated from 24-hour urine collection with predicted creatinine was the most widely used method in the studies reviewed for the guideline.

Although it is clinically inconvenient to collect urine for 24 hours to establish the quantity of protein excreted, the GDG found insufficient evidence to recommend use of a shorter collection period.

The optimal frequency for testing urinary protein was not clear from the evidence and the GDG's view is that it would depend on the degree of hypertension and the presence of risk factors for pre-eclampsia.

Recommendations

Use an automated reagent-strip reading device or a spot urinary protein:creatinine ratio for estimating proteinuria in a secondary care setting.

If an automated reagent-strip reading device is used to detect proteinuria and a result of 1+ or more is obtained, use a spot urinary protein:creatinine ratio or 24-hour urine collection to quantify proteinuria.

Diagnose significant proteinuria if the urinary protein:creatinine ratio is greater than 30 mg/mmol or a validated 24-hour urine collection shows greater than 300 mg protein.

Where 24-hour urine collection is used to quantify proteinuria, there should be a recognised method of evaluating completeness of the sample.

Research recommendation

How should significant proteinuria be defined in women with hypertension during pregnancy?

Why this is important

Most adverse outcomes in new-onset hypertensive disorders during pregnancy arise in women with proteinuria. However, the quality of evidence for the diagnosis of significant proteinuria is poor and the prognostic value of different quantities of urinary protein is unclear. There is a need for large, high-quality prospective studies comparing the various methods of measuring proteinuria (automated reagent-strip reading devices, urinary protein:creatinine ratio, urinary albumin:creatinine ratio, and 24-hour urine collection) in women with new-onset hypertensive disorders during pregnancy. The studies should aim to determine which method of measurement, and which diagnostic thresholds, are most accurate in predicting clinically important outcomes. Such studies would inform decisions regarding clinical management of new-onset hypertensive disorders during pregnancy. If predictive parameters were identified then interventions based on these and aimed at improving outcomes could be evaluated in randomised clinical trials.

6 Management of pregnancy with gestational hypertension

6.1 Introduction

Most women present initially because a raised blood pressure has been identified at a routine antenatal visit. Chapter 5 has dealt with how to distinguish between those with significant proteinuria and those without. This chapter will cover the initial assessment and continuing care of women who have new hypertension but do not have significant proteinuria. The function of the initial assessment is to:

- determine the level of hypertension and whether treatment is required
- consider ancillary tests to guide further care by identifying those women most likely to develop proteinuria (that is, pre-eclampsia) or those with underlying pathology.

6.2 Frequency of blood pressure measurement

No studies were found that provide evidence on the frequency of blood pressure measurements.

6.3 Risk of progression to pre-eclampsia

Clinical risk factors

Evidence on risk factors for pre-eclampsia is discussed in 'Antenatal care', NICE clinical guideline 62.[1]

Gestational age at diagnosis

A retrospective analysis combined with a prospective study ($n = 845$) was conducted in Australia to investigate the progression from gestational hypertension to pre-eclampsia.[95] [EL = 2+] The retrospective analysis ($n = 661$) included women initially diagnosed as having gestational hypertension and the prospective study ($n = 184$) included women with gestational hypertension. Both excluded women with essential hypertension, kidney disease or other secondary causes of hypertension.

Pre-eclampsia was defined as one or more of the following: proteinuria 300 mg/day or higher (or persistently 2+ or more on dipstick urinalysis), renal impairment (plasma creatinine 100 micromol/litre or higher), hepatic dysfunction (aspartate aminotransferase 50 IU/litre or higher and/or severe persistent epigastric pain), haematological abnormalities (haemolysis and/or platelet count below 150×10^9/litre), cerebral disorder (visual scotomata, convulsions, hyper-reflexia when accompanied by clonus) or severe hypertension (systolic blood pressure of 170 mmHg or higher and/or diastolic blood pressure above 110 mmHg). Women with eclampsia were included in the pre-eclampsia group.

In the univariate analysis of the combined data, the following predictors were shown to be statistically significantly associated with progression to pre-eclampsia:

- gestation at presentation with raised blood pressure
- serum albumin
- prior miscarriage.

In the multivariate analysis, the following remained statistically significant:

- gestation at presentation (OR 0.69; 95% CI 0.51 to 0.94)
- prior miscarriage (OR 3.44; 95% CI 1.35 to 8.78)

Serum albumin, recurrent gestational hypertension or pre-eclampsia, haematocrit, plasma creatinine and plasma uric acid were not shown to predict the progression to pre-eclampsia.

One retrospective cohort study was conducted in the USA and described the natural course of mild gestational hypertension remote from term and looked at the prognostic signs for progression of disease to pre-eclampsia.[96] [EL = 2+] The study included 748 women: 343 with mild gestational hypertension with proteinuria (1+ on dipstick on at least two occasions) and 405 women with gestational hypertension without proteinuria. Women with associated medical and obstetric complications other than gestational or chronic hypertension were excluded, as were pregnancies with maternal or fetal compromise, rupture of the membranes or uncontrolled severe hypertension. There were no significant differences in maternal age, race, marital status or tobacco use between those with and those without proteinuria. Gestational age at enrolment (OR 0.92; 95% CI 0.88 to 0.97; $P = 0.004$) and maternal age (OR 0.97; 95% CI 0.94 to 1.00; $P = 0.028$) were statistically significant predictors of proteinuria. BMI (OR 1.02; 95% CI 1.00 to 1.04; $P = 0.091$), parity (OR 1.30; 95% CI 0.91 to 1.84; $P = 0.143$), history of miscarriage (OR 0.99; 95% CI 0.61 to 1.60; $P = 0.953$), systolic blood pressure (OR 1.00; 95% CI 0.98 to 1.01; $P = 0.891$) and diastolic blood pressure (OR 1.00; 95% CI 0.98 to 1.02; $P = 0.747$) were not statistically significant predictors of proteinuria.

One case–control study conducted in the UK studied 560 women with suspected gestational hypertension.[97] [EL = 2–] Gestational age at first presentation of less than 35 weeks as a predictive factor for the development of pre-eclampsia had a sensitivity of 56% and specificity of 69%, with LR+ of 1.80 (95% CI 1.5 to 2.2) and LR– of 0.64 (95% CI 0.5 to 0.8).

Blood tests in the prediction of pre-eclampsia (proteinuria)

Serum uric acid

One EL II study and two EL III studies investigated the predictive value of serum uric acid using various reference standards.[87;97;98]

The Italian study, which evaluated the use of serum uric acid levels to predict proteinuria (pre-eclampsia), included 108 pregnant hypertensive women, of which 40 (37%) had chronic hypertension.[87] [EL = III] The included women were between 28 and 30 weeks of gestation and had less than 300 mg protein in a 24-hour urine sample at the time of sampling. No exclusion criteria were stated. Whether or not the first morning urine void was excluded from the 24-hour collection was not reported. The timing of the tests and whether outcome assessors were blinded to the results was not reported. Serum uric acid levels were compared with 24-hour urine protein excretion. The threshold for the uric acid level was determined by the value of the mean ± 2 SD, which was 0.27 mmol/litre. Sensitivity, specificity and positive and negative LRs were 60% (95% CI 31.3% to 83.2%), 86.7% (95% CI 78.6 % to 92.1%), 4.52 (95% CI 2.21 to 9.25) and 0.46 (95% CI 0.22 to 0.99), respectively.

The UK study investigated the use of serum uric acid levels for predicting significant proteinuria.[98] [EL = III] The study population ($n = 325$) consisted of women referred to the antenatal day unit between March 1992 and the end of July 1993 with a diagnosis of mild hypertension (defined as diastolic blood pressure of 90 mmHg or higher on two separate recordings). Neither exclusion criteria nor details of the timing of the tests were reported. The gold standard was not a standard test but significant proteinuria was defined as 1+ or greater on dipstick. The sensitivity for uric acid levels above 0.40 mmol/litre in primigravid women ($n = 168$) in predicting proteinuria was 7.7% (95% CI 3.0% to 18.2%), the specificity was 95.5% (95% CI 89.9% to 98.1%) and the positive LR and, again, the negative LR were poor. Using a threshold of 0.35 mmol/litre gave similar results. The sensitivity and specificity were 21.2% (95% CI 12.2% to 34%) and 86.5% (95% CI 78.9% to 91.6%) and the LRs were poor. These results were similar to the diagnostic accuracy results seen in multigravid women ($n = 157$).

A case–control study[97] [EL = II] showed that uric acid had a sensitivity of 65% in predicting pre-eclampsia in women with suspected gestational hypertension. It also had a specificity of 47% with LRs (LR+ 1.72, 1.5–2.0; LR– 0.49, 0.3–0.7) at a best predictive z-score value of greater

than 1.3. At a best predictive value of greater than 0.26 mmol/litre, the sensitivity was 65%, specificity 47% and the positive and negative LRS were 1.24 (95% CI 1.01 to 1.5) and 0.74 (95% CI 0.5 to 1.0), respectively.

Platelet count

A study that investigated the predictive value of the platelet count was conducted in the UK and included 325 women with gestational hypertension.[98] [EL = III] All women referred to the antenatal day unit between March 1992 and the end of July 1993 with a diagnosis of mild hypertension defined as diastolic blood pressure of 90 mmHg or higher on two separate recordings without proteinuria were included. No details of the timing of the reference test were reported. Significant proteinuria was defined as 1+ or greater on dipstick. Sensitivity and specificity for a platelet count below 150×10^9/litre were 9.8% (95% CI 4.3% to 21%) and 92.3% (95% CI 86% to 95.9%), respectively, in primigravid women ($n = 168$), and 15.4% (95% CI 7.2% to 29.7%) and 81.4% (95% CI 73.4% to 87.4%), respectively, in multigravid women ($n = 157$). The LRs were poor. Using a threshold of 200×10^9/litre did not improve the effectiveness of the test: sensitivity was 45.1% (95% CI 32.3% to 58.6%) and specificity 62.4% (95% CI 53.4% to 70.6%), while the LRs were poor. The results were similar in multigravid women.

A case–control study[97] [EL = II] showed that platelet count is not a statistically significant predictor of pre-eclampsia in women suspected of having gestational hypertension.

Serum uric acid and platelet count

One study was identified which assessed the value of serum uric acid and platelet count in predicting the need to use a pre-eclampsia management regimen among women with gestational hypertension. The pre-eclampsia regimen was defined as the need for intravenous antihypertensive therapy and anticonvulsant.[98]

The UK study investigated the effectiveness of platelet count and serum uric acid levels and included 325 women with gestational hypertension.[98] [EL = III] All women referred to the antenatal day unit between March 1992 and the end of July 1993 with a diagnosis of mild hypertension defined as diastolic blood pressure of 90 mmHg or higher on two separate recordings were included. No exclusion criteria were stated and nor were details of the timing of the tests reported.

Sensitivity and specificity for a platelet count below 150×10^9/litre for predicting pre-eclampsia in primigravid women were 28.6% (95% CI 8.2% to 64.1%) and 92.5% (95% CI 87.4% to 95.7%), respectively. The positive and negative LRs were 3.83 (95% CI 1.05 to 13.95) and 0.77 (95% CI 0.48 to 1.24), respectively. The sensitivity, specificity and positive and negative LRs for a platelet count below 200×10^9/litre were 50% (95% CI 18.8% to 81.2%), 53.6% (95% CI 45.7% to 61.4%), 1.08 (95% CI 0.48 to 2.45) and 0.93 (95% CI 0.41 to 2.10) in primigravid women, respectively.

The sensitivity for uric acid levels above 0.40 mmol/litre in primigravid women for predicting pre-eclampsia was 6.2% (95% CI 0.7% to 40.2%), the specificity 93.9% (95% CI 89.1% to 96.7%), the positive LR 1.03 (95% CI 0.07 to 16.22) and the negative LR 1.00 (95% CI 0.83 to 1.20). The sensitivity, specificity and positive and negative LRs for uric acid levels above 0.35 mmol/litre in primigravid women were 6.2% (95% CI 0.7% to 40.2%), 83.1% (95% CI 76.5% to 88.2%), 0.37 (95% CI 0.03 to 5.54) and 1.13 (95% CI 0.93 to 1.37), respectively. Essentially, these results do not differ from those derived for multigravid women.

Urea and serum creatinine

A case–control study[97] [EL = II]) showed that in women suspected of having gestational hypertension, creatinine, with the best predictive *z*-score value greater than 0.01, had a sensitivity of 62% and specificity of 49%, with positive and negative LRs of 1.23 (95% CI 1.0 to 1.5) and 0.76 (95% CI 0.6 to 1.0), respectively.

Liver function tests

A case–control study[97] [EL = II]) showed that in women suspected of having gestational hypertension, alanine aminotansferase (ALT) measure was not a statistically significant predictor of pre-eclampsia.

Coagulation and clotting tests

No evidence was found for coagulation and clotting tests.

Blood pressure

A case–control study[97] [EL = II] showed that in women with suspected gestational hypertension, systolic blood pressure was found to have a sensitivity of 64% in predicting pre-eclampsia. It also had a specificity of 65%, with statistically significant positive and negative LRs of 1.85 (95% CI 1.6 to 2.3) and 0.55 (95% CI 0.4 to 0.8), respectively, with a best predictive *z*-score value greater than 3.2. With a best predictive absolute value of greater than 135 mmHg, the sensitivity of systolic blood pressure in predicting pre-eclampsia was 62% and specificity was 54%, with statistically significant positive and negative LRs or 1.4 (95% CI 1.1 to 1.6) and 0.69 (95% CI 0.5 to 0.9), respectively. Diastolic blood pressure had a sensitivity of 45% and specificity of 80%, with statistically significant positive and negative LRs of 2.33 (95% CI 1.8 to 2.9) and 0.68 (95% CI 0.5 to 0.9), respectively, at a best predictive *z*-score value of greater than 3.5. With a best predictive absolute value of greater than 83 mmHg, sensitivity was 89% and specificity 24%, with statistically significant positive and negative LRs of 1.18 (95% CI 1.0 to 1.4) and 0.44 (95% CI 0.2 to 0.8), respectively.

Evidence statement

Gestational age at diagnosis

Three studies investigated the effect of gestational age at diagnosis and progression from gestational hypertension to pre-eclampsia. These showed a statistically significant association between the development of pre-eclampsia and gestation at presentation. One study showed an association with previous miscarriage.

In one study, women with gestational hypertension and a prior miscarriage were nearly 3.5 times more likely to progress to pre-eclampsia than women who did not have a prior miscarriage. The association with miscarriage was only evident in the retrospective study. In addition, women who presented later in pregnancy with gestational hypertension were less likely to progress to pre-eclampsia.

One retrospective cohort study [EL = 2+] looked at predicting whether women with gestational hypertension would develop proteinuria. It found that gestational age at enrolment and maternal age were statistically significant predictors of proteinuria. BMI, parity, history of miscarriage, systolic blood pressure and diastolic blood pressure were not found to be statistically significant predictors of proteinuria.

One case–control study [EL = II] looked at the ability of various indices to predict pre-eclampsia in women with suspected gestational hypertension. Gestational age at first presentation of less than 35 weeks had a sensitivity of 56%, a specificity of 69%.

Blood tests in the prediction of pre-eclampsia (proteinuria)

Serum uric acid

Three studies investigated the diagnostic value of serum uric acid levels for predicting proteinuria and hence the diagnosis of pre-eclampsia. One study with EL III reported a low sensitivity (60%) and a high specificity (87%). Another study with the same evidence level used 1+ or greater on dipstick as the reference standard. This study showed serum uric acid to have a very poor sensitivity (8%) and a very high specificity (96%) in primigravid women and similar results in multigravid women. Lowering the threshold lowered the results slightly and led to a sensitivity of 21% and a specificity of 87% in primigravid women. The results were similar in multigravid women. The second study showed a weak relationship between uric acid levels corrected for gestation and progression but the authors did not feel that the link was sufficient to consider use of uric acid.

One case–control study [EL = II] looked at the ability of different indices to predict pre-eclampsia in women with suspected gestational hypertension. It showed that uric acid had a sensitivity of 65%, specificity of 47% and statistically significant LRs (LR+ 1.24; 95% CI 1.01 to 1.5, LR– 0.74; 95% CI 0.5–1.0).

Platelet count

One study [EL = III] showed platelet count to be of little diagnostic value. The reference test used was 1+ or greater on dipstick. When using a threshold of 150 × 10^9/litre, the sensitivity was below 10% although the specificity was 92%. Using a higher threshold (200 × 10^9/litre) resulted in poor sensitivity (45%) and poor specificity (62%).

A second study could not demonstrate a relationship between maternal platelet count at diagnosis and subsequent pre-eclampsia or IUGR. This case–control study [EL = II] looked at the ability of different indices to predict pre-eclampsia in women with suspected gestational hypertension. It showed that platelet measure is not a statistically significant predictor of pre-eclampsia in women suspected of having gestational hypertension.

Serum uric acid and platelet counts

One study investigated the effectiveness of platelet count and serum uric acid for predicting pre-eclampsia among women with gestational hypertension. Using the threshold 150 × 10^9/litre, the sensitivity for platelet count was very poor (29%) while specificity was very high (93%). Using a threshold of 200 × 10^9/litre gave sensitivity and specificity of around 50%. Serum uric acid had a very poor sensitivity (below 10%) and a good specificity (between 83% and 94%) using 0.40 mmol/litre and 0.35 mmol/litre thresholds.

Urea and serum creatinine

One study [EL = II]) showed that creatinine had a sensitivity of 62% and specificity of 49%, with positive and negative LRs of 1.23 (95% CI 1.0 to 1.5) and 0.76 (95% CI 0.6 to 1.0), respectively, in women suspected of having gestational hypertension.

Liver function tests

One study [EL = II]) showed that ALT did not predict pre-eclampsia in women suspected of having gestational hypertension.

Coagulation and clotting tests

No evidence was found for coagulation and clotting tests.

Blood pressure

One case–control study [EL = II] looked at the ability of various indices to predict pre-eclampsia in women with suspected gestational hypertension. It showed that systolic blood pressure had a sensitivity of 62–64%, specificity of 54–65% (depending on the predictive value used) and statistically significant LRs. Diastolic blood pressure had a sensitivity of 45–89%, specificity of 24–80% and statistically significant LRs.

Cost effectiveness

There were no economic evaluations that considered the cost-effectiveness of the various blood tests in predicting pre-eclampsia. Given the GDG's view that none of the tests are very useful in predicting pre-eclampsia, and the desire to see a rational use of the tests, a simple costing of the proposed use of these tests in women with mild to moderate gestational hypertension was undertaken. The weekly monitoring costs are about £30, £65 and £371 for women with mild, moderate and severe hypertension, respectively. See Tables K.2 and K.3 in Appendix K for the inputs to the costing.

GDG interpretation of the evidence

The frequency of blood pressure measurement will depend on the degree of hypertension and may also be influenced by history and assessment of risk factors. The risk of CVA is increased in more severe hypertension and blood pressure should be recorded more frequently to detect rises in blood pressure and response to therapy.

The evidence concerning the gestation at diagnosis is difficult to interpret. The absence of week-by-week censoring makes it difficult to determine whether early presentation is an inherently riskier condition or whether the increased risk is simply a factor of the time over which severe disease can develop. Absence of that information makes advice on differing care by gestation at presentation difficult. The UK study's finding of an association between gestation at presentation

and IUGR does add credence to a view that early presentation may represent different pathology. However, late-onset gestational hypertension may progress to severe pre-eclampsia. Overall, the GDG agrees with the suggestion of Anumba *et al.*[97] that presentation before 35 weeks merits special consideration.

There is poor-quality evidence to inform the role of biochemical and haematological assessment in women with new-onset hypertension and no proteinuria. None of the commonly used tests appear to predict progression to pre-eclampsia. However, even though these tests are not good at predicting pre-eclampsia, the GDG feels that a negative test is also an important finding as it would indicate non-progression of the disease process.

In spite of the poor evidence base, the GDG feels that the current use of investigations should be rationalised in terms of which tests should be used and how frequently they should be used, rather than discontinued entirely. The generally high specificity of tests may help to rule out likely disease progression. In addition, not all women with pre-eclampsia or its variants have proteinuria and a small number may have underlying disease. The GDG feels that limited use of some blood tests is warranted, especially in the presence of more severe hypertension.

The assessment of new-onset hypertension in pregnancy cannot be made in isolation but should also be seen in context with clinical signs and symptoms, gestational age, and the presence of risk factors for pre-eclampsia. Management protocols may need to be modified in the presence of risk factors. The GDG's view is that pregnant women with any degree of new-onset hypertension, wherever diagnosed, require full assessment in a secondary care setting by a healthcare professional who is trained in the management of hypertensive disorders.

Recommendations

See the end of Section 6.5.

6.4 Prevention of pre-eclampsia

Clinical effectiveness

Antiplatelet agents

Low-dose aspirin

An RCT on the effectiveness of low-dose aspirin for the prevention of pre-eclampsia in women with gestational hypertension was conducted in Israel.[99] [EL = 1+] The study population consisted of 47 nulliparous women at between 30 and 36 weeks of gestation with a diagnosis of mild pregnancy-induced hypertension (defined as a systolic blood pressure between 140 and 165 mmHg and/or diastolic blood pressure between 90 and 110 mmHg, on at least two occasions at least 6 hours apart, and with no signs of moderate to severe pregnancy-induced hypertension such as a low platelet count (less than 105×10^9/litre) or proteinuria of more than 500 mg/day within 24 hours of admission). Women who had a known sensitivity to aspirin, chronic hypertension, a chronic kidney disorder or antihypertensive treatment before admission were excluded. Twenty-three women were randomly allocated to receive aspirin 100 mg/day and 24 women to receive a placebo. No further information about the randomisation method was given. Antihypertensive treatment was started when severe pre-eclampsia was diagnosed.

No statistically significant differences between the treatment and the placebo groups were found for progression to moderate or severe pre-eclampsia (six of 23 versus six of 24, RR 1.04; 95% CI 0.39 to 2.77), gestational age at delivery, newborn weight, newborn percentile or 5-minute Apgar score.

A Cochrane systematic review reported a 40% reduction in the relative risk of progressing to pre-eclampsia in women with gestational hypertension who received antiplatelet agents compared with placebo or no treatment.[41] [EL = 1++]

Evidence statement

An RCT found no statistically significant differences between groups that received aspirin and those that received placebo for progression to moderate or severe pre-eclampsia. A Cochrane

review, however, reported a 40% reduction in the relative risk of progressing to pre-eclampsia in women with gestational hypertension taking aspirin compared with placebo or no treatment.

GDG interpretation of the evidence

The GDG does not consider that the evidence on aspirin supports its use in women with gestational hypertension unless they are at risk of pre-eclampsia as defined in Section 3.2, and so the GDG made no specific recommendation about aspirin prophylaxis for women with gestational hypertension.

6.5 Treatment of hypertension

Although there is a systematic review on the treatment of hypertension during pregnancy,[100] the analyses did not precisely coincide with the questions the guideline needed to address and, therefore, the publications identified in the review were obtained and re-analysed for this guideline (see Tables 6.1 and 6.2).

Evidence in this section is presented from trials involving only women with gestational hypertension, followed by presentation of trials where there appeared to be a mixture of women with gestational and chronic hypertension or where the exact nature of the hypertensive disorder was uncertain.

Clinical effectiveness

Studies of gestational hypertension only

Alpha- and beta-blockers

Two trials published in four articles investigated the effectiveness of labetalol versus placebo (see Table 6.1a).[101-104] [EL = 1–] One trial reported that statistically significantly fewer women taking labetalol developed severe hypertension compared with women taking placebo (RR 0.35; 95% CI 0.14 to 0.92).[101;102] The other trial reported no statistically significant effects for any of the maternal or fetal outcomes.[103;104]

No statistically significant results were found when these two studies were combined in the meta-analysis.

Two studies investigated the effectiveness of beta-blockers compared with placebo.[105;106] [EL = 1–] One study[105] found that among women who received atenolol, fewer were admitted to hospital before giving birth compared with women who received no treatment (RR 0.41; 95% CI 0.27 to 0.62). The other study[106] investigated the effectiveness of oxprenolol but failed to show any statistically significant results.

The combined results for beta-blocker versus placebo showed that treatment with beta-blockers led to a statistically significant reduction in the risk of severe hypertension (pooled RR 0.38; 95% CI 0.17 to 0.89). None of the other combined results were statistically significant.

Methyldopa

A quasi-randomised trial compared labetalol versus methyldopa and found that fewer women who received labetalol developed proteinuria (proteinuria was not defined in the study) compared with women who received methyldopa (RR 0.04; 95% CI 0.003 to 0.73).[107] [EL = 1–]

The presence of proteinuria was the only statistically significant result from this study but it should be interpreted with caution because of the lack of randomisation and the general low quality.

Studies with mixed populations

Methyldopa

An RCT of low quality compared early treatment with methyldopa (before 28 weeks of gestation) versus no specific treatment or late treatment (after 28 weeks).[108] [EL = 1–] Women in the 'no-treatment' group received long-term antihypertensive treatment if they developed severe hypertension. If necessary, other drugs such as hydralazine were given in addition to methyldopa but beta-blockers and diuretics were not used. The population included 242

women before 36 weeks with moderate hypertension, and included women with gestational and with chronic hypertension. The study was not blind and no information on the randomisation method was given. The women were allocated to either the early-treatment group ($n = 208$) or the late-treatment group ($n = 34$). Each of these groups was split into treatment and no-treatment groups. This resulted in 107 women being in the early-treatment group and 101 women in the early no-treatment group, and 18 women being in the late-treatment group and 16 in the late control group who did not receive treatment.

The only statistically significant outcome showed that women treated with methyldopa after 28 weeks had on average an 8 days longer gestation than women who did not receive treatment (late control: 264 ± 13 days; late treated: 272 ± 11 days). No statistically significant differences were found between treatment and control group (early and late) for proteinuria (more than 100 mg/dl), mean birthweight, increase in plasma urate, oedema scores or weight gain.

Further results from the same study described above were reported in another publication.[79] Combining the late-treatment with the early-treatment group, and comparing this wih the combined late and early control group, the study found the incidence of the maximum diastolic blood pressure being at or above 110 mmHg to be lower in the treated women compared with women who were untreated or treated late (RR 0.31; 95% CI 0.17 to 0.58). There were a similar number of women in both groups who reported depression (58% of those in the treatment group and 56% of those in th control group; exact incidence and *P* value not reported). Of the three major psychiatric episodes requiring inpatient treatment, one involved a woman in the methyldopa group and two involved women in the control group.

Hydralazine and other treatments

One low-quality study[109] compared metoprolol in combination with hydralazine with no treatment. [El = 1 –] No statistically significant results were obtained in this study (Table 6.2a).

Another very small low-quality study[110] investigated the effectiveness of hydralazine compared with a combination of hydralazine with propranolol or a combination of hydralazine with pindolol. None of the obtained results were statistically significant (Table 6.2b).

Alpha- and beta-blockers

Two low-quality studies[111;112] investigated labetalol versus methyldopa and one study[113] compared labetalol versus hydralazine. No statistically significant results were reported for any of these three studies (Table 6.2b).

Beta-blockers and placebo

Two studies[114;115] compared beta-blockers with placebo. The study that investigated metoprolol did not show any statistically significant results. The other study[115] showed that fewer women developed severe hypertension when given pindolol when compared with women who received a placebo.

One small low-quality study ($n = 51$) compared atenolol with pindolol.[116] [EL = 1 –] The only outcome of interest reported was severe hypertension, which was not statistically significant (Table 6.2b).

Beta-blockers and methyldopa

Five studies[117-122] compared the effectiveness of various beta-blockers with methyldopa. No statistically significant results were found in any of these studies to indicate whether one drug was more effective than another (Table 6.2b).

The pooled analysis for the comparisons of beta-blockers with placebo or with other antihypertensive drugs showed no statistically significant results. Pooling the results of labetalol versus other antihypertensive therapy with results from studies comparing beta-blockers with other antihypertensive therapy did not show any statistically significant results either.

Beta-blockers and calcium-channel agents

One RCT conducted in France compared the effectiveness of nicardipine with that of metoprolol.[123] [EL = 1 –] One hundred women with singleton pregnancies and mild or moderate hypertension and who were at least 20 weeks pregnant were included in the study. Hypertension was defined as systolic blood pressure of 140 mmHg or higher and/or a diastolic

blood pressure of 90 mmHg or higher. None of the included women had received other antihypertensive medication before entry to the study. Fifty women were randomly allocated to receive 20 mg oral nicardipine three times a day and 50 women to receive 200 mg oral slow-release metoprolol once a day. Whether the participants and/or investigators were blinded to who received which treatment was not mentioned. Women receiving nicardipine showed statistically significantly lower systolic and diastolic blood pressure compared with women who received metoprolol. No statistically significant results were found for any of the other investigated outcomes (Table 6.2b).

The meta-analysis for the comparison of beta-blockers with other antihypertensive treatments included seven studies. For the outcomes severe hypertension (three studies), perinatal mortality (six studies), proteinuria at delivery (five studies) and admission to special care baby unit (two studies), no statistically significant results were found. Owing to the small number of available studies, no meta-analysis could be conducted for the following outcomes: eclampsia/HELLP syndrome, maternal death, admission to HDU/ICU or small for gestational age.

Calcium-channel agents and methyldopa

An RCT conducted in Sri Lanka compared the effectiveness of nifedipine with methyldopa.[124] [EL = 1–] A total of 126 women were included. The inclusion criteria were systolic blood pressure of 140 mmHg or higher, a diastolic blood pressure of 90 mmHg or higher on two occasions 12 hours apart, normal blood pressure before pregnancy, being normotensive at booking and no previous history of kidney, vascular or collagen disease. Selected women were alternately allocated to receive either nifedipine 30–90 mg/day or methyldopa 750–2000 mg/day.

Apgar score was better for infants of women who received methyldopa. More women needed treatment for acute hypertension in the nifedipine group compared with women who received methyldopa and this difference was statistically significant (RR 1.67; 95% CI 1.16 to 2.40). No statistically significant differences were found for the incidence of placental abruption, HELLP syndrome, eclampsia, caesarean section, maternal side effects, birthweight, intrauterine death or maturity at delivery.

One study conducted in Italy compared verapamil with two different beta-blockers (pindolol and atenolol).[125] [EL = 1–] A total of 94 women were included. For the comparison of verapamil with pindolol, there were 22 women in each group. For the comparison of verapamil with atenolol, there were 25 women in each group. There were no perinatal deaths in the verapamil, pindolol or atenolol groups (RR not estimable).

Evidence statement

In the majority of included studies examining the effect of antihypertensive agents, the population was either not clearly defined or included a mixed population, with various combinations of women with and without proteinuria, and women with gestational hypertension and/or with chronic hypertension.

Overall, seven studies[73;100-102;104;105;107] were included for women with gestational hypertension alone. No suitable studies were identified for antihypertensive treatment such as methyldopa, prazosin and hydralazine, for calcium-channel blockers or for diuretics. Five small studies [EL = 1–] investigated the effectiveness of alpha- and beta-blockers. One study[101] found labetalol to lower the incidence of severe hypertension compared with placebo, whereas another[105] found beta-blockers to lower the rate of hospital admission before birth compared with placebo. One quasi-randomised study[107] found labetalol to lower the incidence of pre-eclampsia compared with methyldopa.

Overall, 19 studies [El = 1–] and a mixed study population were included. No studies were identified for the following interventions: diuretics, platelets and rest or bed rest. Three studies compared labetalol with methyldopa and one study that compared labetalol with hydralazine did not show any statistically significant result. Two studies investigated beta-blockers compared with placebo but only one study showed a statistically significant result. Beta-blockers in this study were found to lower the incidence of severe hypertension. Five trials compared beta-blockers with methyldopa, one study compared them with nicardipine and one study compared

them with another beta-blocker. One study compared metoprolol plus hydralazine with no treatment and another study compared hydralazine with hydralazine combined with propanolol or with pindolol. One study compared verapamil with two different beta-blockers and another study compared methyldopa with no specific treatment. None of these studies achieved any statistically significant results. One study found nifedipine to be less effective than methyldopa in the prevention of severe hypertension. This result was statistically significant.

Treatment for hypertension with different target blood pressures

This evidence is presented in Section 4.4.2.

Rest/bed rest

An RCT was conducted in Zimbabwe to compare the effectiveness of hospital admission for bed rest with continuation of normal activities at home.[73] [EL = 1+] Two hundred and eighteen women with singleton pregnancies with blood pressure of 140/90 mmHg or higher, without proteinuria and between 28 and 38 weeks of gestation were included in this study. Women who were symptomatic, had a diastolic blood pressure of 100 mmHg or higher, a caesarean section scar or an antepartum haemorrhage during the pregnancy were excluded. The study population included women with chronic hypertension. The results reported here are for women with gestational hypertension only (hospital rest group: $n = 95$; normal activities at home group: $n = 90$). The outcome assessors were not blinded for the outcomes blood pressure and proteinuria but were they blinded for all other outcomes.

In all of the 218 women (including those with chronic hypertension), hospital admission for bed rest reduced the risk of preterm birth before 37 weeks (OR 0.48; 95% CI 0.24 to 0.97). Bed rest also reduced the risk of developing severe hypertension (OR 0.52; 95% CI 0.27 to 0.99) in the subgroup of women with gestational hypertension. However, no statistically significant differences were found between women who had hospital bed rest and those who continued normal activities at home in relation to other outcomes reported (mean duration of hospital stay, gestational age at delivery, preterm birth before 34 weeks, development of proteinuria or severe proteinuria, incidence of SGA babies, or admission to a neonatal unit).

Table 6.1a Reported results of treatment for women with gestational hypertension – intervention compared with placebo (reported as RRs or ORs with 95% CIs)

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Labetalol versus placebo									
Pickles *et al.* (1989,1992)[101;102] [EL = 1–] UK	5/70 versus 15/75 RR 0.35 (0.14 to 0.92)	17/70 versus 24/74 RR 0.75 (0.44 to 1.27)	–	–	–	0/70 versus 0/74 not estimable	10/70 versus 5/74 RR 2.11 (0.76 to 5.88)	12/70 versus 17/74 RR 0.75 (0.38 to 1.45)	10/70 versus 9/74 RR 1.17 (0.51 to 2.72)
Cruickshank *et al.* (1991, 1992)[103;104] [EL = 1–] UK	–	13/51 versus 17/63 RR 0.94 (0.51 to 1.76)	–	–	–	0/51 versus 2/63 RR 0.25 (0.01 to 5.02)	6/51 versus 5/63 RR 1.48 (0.48 to 4.58)	10/51 versus 13/63 RR 0.95 (0.45 to 1.99)	18/51 versus 17/63 RR 1.31 (0.79 to 2.00)
Beta-blocker versus placebo									
Rubin *et al.* (1983)[105] (Atenolol) [EL = 1–] UK	2/60 versus 7/60 RR 0.29 (0.06 to 1.32)	13/60 versus 21/60 RR 0.62 (0.34 to 1.12)	–	–	16/46 versus 3/39 RR 0.41 (0.27 to 0.62)	1/60- versus 2/60 RR 0.49 (0.04 to 5.57)	9/59 versus 8/58 RR 1.11 (0.46 to 2.67)	9/59 versus 8/58 RR 1.11 (0.46 to 2.67)	–
Plouin *et al.* (1990)[106] (Oxprenolol) [EL = 1–] France	5/78 versus 11/76 RR 0.44 (0.16 to 1.21)	7/78 versus 7/72 RR 0.92 (0.34 to 2.50)	0/78 versus 0/76 not estimable	1/78 versus 0/76 RR 2.92 (0.13 to 70.68)	48/78 versus 46/76 RR 1.02 (0.79 to 1.31)	2/78 versus 3/76 RR 0.64 (0.10 to 3.94)	7/78 versus 9/76 RR 1.11 (0.46 to 2.67)	11/78 versus 14/76 RR 0.77 (0.37 to 1.58)	16/76 versus 24/75 RR 0.66 (0.38 to 1.14)

HDU = high-dependency unit; HELLP = haemolysis, elevated liver enzymes and low platelet count; ICU = intensive care unit; NICU = neonatal intensive care unit; SGA = small for gestational age

Table 6.1b Reported results of treatment for women with gestational hypertension – comparison of two interventions (reported as RRs or ORs with 95% CIs)

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Labetalol versus methyldopa									
El-Qarmalawi *et al.* (1995)[107] [EL = 1 –] Kuwait	1/54 versus 3/50 RR 0.31 (0.03 to 2.87)[a]	0/54 versus 10/50 RR 0.04 (0.003 to 0.73)	–	–	–	–	–	3/54 versus 3/50 RR 0.93 (0.20 to 4.38)[b]	–
Bed rest versus normal activities at home									
Crowther *et al.* (1992)[73] [EL = 1 +] Zimbabwe	22/95 versus 33/90 OR 0.52 (0.27 to 0.99)	58/95 versus 56/90 OR 0.95 (0.53 to 1.72)	–	–	–	–	12/95 versus 14/90 OR 0.78 (0.34 to 1.80)	–	–

HDU = high-dependency unit; HELLP = haemolysis, elevated liver enzymes and low platelet count; ICU = intensive care unit; NICU = neonatal intensive care unit; SGA = small for gestational age

[a] Preterm labour

Table 6.2a Reported results of treatment for hypertension for mixed populations – intervention compared with placebo (reported as RRs or ORs with 95% CIs)

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Beta-blocker versus placebo									
Wichman *et al.* (1984)[114] (Metoprolol) [EL = 1–] Sweden	1/26 versus 0/26 RR 3.00 (0.13 to 70.42)	11/26 versus 11/26 RR 1.00 (0.53 to 1.89)	–	0/26 versus 0/26 not estimable	16/26 versus 19/26 RR 0.84 (0.57 to 1.24)	0/26 versus 1/26 RR 0.32 (0.39 to 7.03)	–	–	–
Bott-Kanner *et al.* (1992)[115] (Pindolol) [EL = 1–] Israel	6/30 versus 15/30 RR 0.40 (0.18 to 0.89)	2/30 versus 5/30 RR 0.40 (0.08 to 1.90)	–	–	–	1/30 versus 0/30 RR 2.93 (0.30 to 28.73)	–	–	–
Methyldopa versus no specific treatment									
Redman *et al.* (1976)[108,79] [EL = 1–] UK	–	Not significant	–	–	–	–	–	–	–
Metroprolol plus hydralazine versus no treatment									
Högstedt *et al.* (1985)[109] [EL = 1–] Sweden	–	10/86 versus 6/82 RR 1.59 (0.60 to 4.17)	–	–	–	3/86 versus 1/82 RR 2.93 (0.30 to 28.73)	6/83 versus 4/81 RR 1.46 (0.43 to 5.00)	23/83 versus 20/81 RR 1.12 (0.67 to 1.88)	–

HDU = high-dependency unit; HELLP = haemolysis, elevated liver enzymes and low platelet count; ICU = intensive care unit; NICU = neonatal intensive care unit; SGA = small for gestational age

Table 6.2b Reported results of treatment for hypertension for mixed populations – comparison between two interventions (reported as RRs or ORs with 95% CIs)

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Labetalol versus methyldopa									
Redman *et al.* (1977)[79] [EL = 1–] UK and Ireland	–	19/39 versus 10/35 RR 1.71 (0.92 to 3.15)	–	–	–	–	13/38 versus 15/34 RR 0.78 (0.43 to 1.39)	–	19/39 versus 16/35 RR 1.07 (0.66 to 1.73)
Lamming *et al.* (1980)[111] [EL = 1–] UK	0/14 versus 2/12 RR 0.17 (0.01 to 3.29)	5/14 versus 9/12 RR 0.48 (0.22 to 1.03)	–	–	–	0/14 versus 0/12 not estimable	–	–	–
Plouin *et al.* (1988)[112] [EL = 1–] France	–	8/91 versus 8/85 RR 0.93 (0.37 to 2.38)	–	–	44/91 versus 46/85 RR 0.89 (0.67 to 1.19)	1/91 versus 4/85 RR 0.23 (0.03 to 2.05)	11/91 versus 12/81 RR 0.82 (0.38 to 1.75)	22/91 versus 21/85 RR 0.98 (0.58 to 1.65)	34/91 versus 29/81 RR 1.04 (0.70 to 1.55)
Hydralazine versus hydralazine plus propranolol or pindolol									
Paran *et al.* (1995)[110] [EL = 1–] Israel	–	–	0/36 versus 0/15 not estimable	–	–	0/36 versus 0/15 not estimable	13/36 versus 4/15 RR 1.35 (0.53 to 3.48)	10/36 versus 3/15 RR 1.39 (0.44 to 4.35)	–
Labetalol versus hydralazine									
Hjertberg *et al.* (1993)[113] [EL = 1–] Sweden	9/9 versus 7/11 RR 1.52 (0.96 to 2.41)	–	–	–	–	0/9 versus 1/11 RR 0.40 (0.02 to 8.78)	3/9 versus 8/11 RR 0.46 (0.17 to 1.24)	–	–
Beta-blocker versus beta-blocker									
Tuimala *et al.* (1988)[116] (Atenolol versus pindolol) [EL = 1–] Finland	3/24 versus 4/27 RR 0.84 (0.21 to 3.40)	–	–	–	–	–	–	–	–

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Beta-blocker versus methyldopa									
Fidler *et al.* (1983)[117] (Oxprenolol) [EL = 1–] UK	–	7/50 versus 7/50 RR 1.00 (0.38 to 2.64)	–	–	39/48 versus 36/48 RR 1.08 (0.88 to 1.34)	1/50 versus 1/50 RR 1.00 (0.06 to 15.55)	–	–	–
Gallery *et al.* (1979)[118,119] (Oxprenolol) [EL = 1–] Australia	10/96 versus 10/97 RR 0.91 (0.40 to 2.07)	10/96 versus 10/87 RR 0.91 (0.40 to 2.07)	–	–	–	1/96 versus 3/87 RR 0.30 (0.03 versus 2.85)	–	–	15/95 versus 19/87 RR 0.72 (0.39 to 1.33)
Oumachigui *et al.* (1992)[120] (Metoprolol) [EL = 1–] India	–	–	–	–	–	1/16 versus 3/15 RR 0.31 (0.04 to 2.68)	–	0/15 versus 3/14 RR 0.13 (0.01 to 2.38)	–
Livingstone *et al.* (1983)[121] (Propranolol) [EL = 1–] Australia	1/14 versus 0/14 RR 3.00 (0.13 to 67.91)	6/14 versus 4/14 RR 1.50 (0.54 to 4.18)	–	–	–	0/14 versus 0/14 not estimable	–	6/14 versus 4/14 RR 1.50 (0.54 to 4.18)	–
Ellenbogen *et al.* (1986)[122] (Pindolol) [EL = 1–] Israel	–	4/16 versus 9/16 RR 0.44 (0.17 to 1.15)	0/16 versus 0/16 not estimable	–	–	1/16 versus 1/16 RR 1.00 (0.07 to 14.64)	–	–	–
Beta-blocker versus calcium-channel blocker nicardipine									
Jannet *et al.* (1994)[123] (Metoprolol) [EL = 1–] France	15/50 versus 7/50 RR 2.14 (0.96 to 4.80)	8/50 versus 3/50 RR 2.67 (0.75 to 9.47)	–	–	–	1/50 versus 1/50 RR 1.00 (0.06 to 15.55)	–	–	6/50 versus 4/50 RR 1.50 (0.45 to 4.99)

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Calcium-channel blocker verapamil versus beta-blocker									
Marlettini *et al.* (1990)[125] (Pindolol) [EL = 1–] Italy	–	–	–	–	–	0/22 versus 0/22 not estimable	–	–	–
Marlettini *et al.* (1990)[125] (Atenolol) [EL = 1–] Italy	–	–	–	–	–	0/25 versus 0/25 not estimable	–	–	–
Calcium-channel blocker versus methyldopa									
Jayawardana *et al.* (1994)[124] (Nifedipine) [EL = 1–]	40/63 versus 24/63 RR 1.67 (1.16 to 2.40)[a]	–	1/63 versus 1/63 RR 1.00 (0.06 to 15.64)[b]	–	–	–	–	–	–

HDU = high-dependency unit; HELLP = haemolysis, elevated liver enzymes and low platelet count; ICU = intensive care unit; NICU = neonatal intensive care unit; SGA = small for gestational age

[a] The outcome reported was need for treatment for acute hypertension

[b] The outcome reported was HELLP syndrome

Evidence statement

A small but well-conducted RCT [EL = 1+] in Zimbabwe found hospital bed rest compared with normal activities at home to be effective in preventing progression to severe hypertension in women with gestational hypertension.

GDG interpretation of the evidence

Treatment with antihypertensive agents

Limited good -quality evidence is available in relation to treatment of gestational hypertension. The available evidence does not support blood pressure lowering treatment for mild or moderate gestational hypertension as a means of improving pregnancy outcomes compared with starting treatment once severe hypertension has developed.

However ,the evidence base is not large enough to know whether antihypertensive treatment prevents uncommon outcomes such as maternal CVA or placental abruption. There is also insufficient evidence about the appropriate level of blood pressure to be aimed for by treatment: it must be low enough to prevent secondary damage such as CVAs without being excessively low and thereby inducing reduced growth of the baby.

There is good evidence to show that beta-blockers and drugs such as labetalol reduce the risk of severe hypertension. One small poor-quality study found a statistically significant reduction in the risk of pre-eclampsia/proteinuria with labetalol compared with methyldopa. There was little evidence on the use of calcium-channel blockers.

The GDG considered the suggested association between maternal treatment with beta-blockers and fetal growth and neonatal beta-blockade, and their consensus was that the reported adverse effects were likely to be dose related and as a result of excessive lowering of blood pressure.

Labetalol appears to be as effective and safe as other antihypertensive agents for managing gestational hypertension and, as it is licensed for use in pregnancy, the GDG's view is that labetalol should be used as first-line treatment in this group of women. All NICE clinical guidelines assume that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. The GDG's view is that a specific recommendation should be included in this guideline to highlight alternatives to labetalol, including methyldopa and nifedipine, to be offered after considering side-effect profiles for the woman, fetus and newborn baby. In making this recommendation, the GDG noted concern over the possibility of reduced effectiveness of labetalol in women of Afro-Caribbean origin who do not respond well to beta-blockers. Although this effect is recognised outside pregnancy, and the GDG was not aware of any evidence that of it being repeated in pregnancy, the recommendation to consider alternative antihypertensive treatment covers this group of women, as well as those for whom labetalol is contraindicated (for example, women with asthma).

Bed rest

The evidence in relation to bed rest comes from a small RCT that examined the effectiveness of hospital bed rest in women with gestational hypertension. Although the study found that hospital bed rest was more effective than continuing normal activities at home, it was conducted in a healthcare setting that was not applicable to the UK. Prolonged bed rest can increase the risk of venous thromboembolism and so the GDG advises against admission to hospital for bed rest.

Recommendations

In women with gestational hypertension full assessment should be carried out in a secondary care setting by a healthcare professional who is trained in the management of hypertensive disorders.

In women with gestational hypertension, take account of the following risk factors that require additional assessment and follow-up:

- nulliparity
- age 40 years or older
- pregnancy interval of more than 10 years
- family history of pre-eclampsia
- multiple pregnancy
- BMI of 35 kg/m² or more
- gestational age at presentation
- previous history of pre-eclampsia or gestational hypertension
- pre-existing vascular disease
- pre-existing kidney disease.

Offer women with gestational hypertension an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in the table below

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	No	No	Yes (until blood pressure is 159/109 mmHg or lower)
Treat	No	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg
Measure blood pressure	Not more than once a week	At least twice a week	At least four times a day
Test for proteinuria	At each visit using automated reagent-strip reading device or urinary protein : creatinine ratio	At each visit using automated reagent-strip reading device or urinary protein : creatinine ratio	Daily using automated reagent-strip reading device or urinary protein : creatinine ratio
Blood tests	Only those for routine antenatal care	Test kidney function, electrolytes, full blood count, transaminases, bilirubin Do not carry out further blood tests if no proteinuria at subsequent visits	Test at presentation and then monitor weekly: • kidney function, electrolytes, full blood count, transaminases, bilirubin

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Only offer women with gestational hypertension antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine.†

In women receiving outpatient care for severe gestational hypertension, after it has been effectively controlled in hospital, measure blood pressure and test urine twice weekly and carry out weekly blood tests.

In women with mild hypertension presenting before 32 weeks, or at high risk of pre-eclampsia, measure blood pressure and test urine twice weekly.

Do not offer bed rest in hospital as a treatment for gestational hypertension.

Research recommendation

What is the role of assessing haematological or biochemical parameters at diagnosis of gestational hypertension and during surveillance of gestational hypertension?

Why this is important

Pre-eclampsia is a multisystem disorder, but it is not clear whether routine assessment of a range of haematological or biochemical parameters in women with gestational hypertension helps clinical care or is sufficiently discriminatory to allow better targeted care. Information on which assessments might be useful is incomplete and there are confusing data on whether clinical outcomes are changed.

Large prospective studies should be carried out to examine a range of parameters singly and serially (kidney function, liver function, coagulation, measurement of proteinuria) in women with gestational hypertension. These studies should use properly validated pregnancy values and examine the prediction of clinically important outcomes (severe pre-eclampsia and its maternal and fetal complications).

If parameters with sufficient prediction are identified, randomised controlled trials should be used to compare the effect of knowledge of these compared with no knowledge on clinical maternal and perinatal outcomes. Trial results should be incorporated in health economic models to assess cost effectiveness.

6.6 Fetal monitoring

Clinical effectiveness

See Chapter 8.

GDG interpretation of the evidence

There are no studies that examine fetal surveillance in a population that only includes women with gestational hypertension and therefore inference on surveillance has to be made from general studies of high-risk pregnancies.

There was a lack of relevant evidence for the use of biometry in hypertensive disorders. There does seem to be evidence that early-onset gestational hypertension carries an increased risk of IUGR and the GDG felt that it would be reasonable to consider biometry in this group.

Although the single study on umbilical artery Doppler velocimetry that dealt with hypertensive pregnancies appeared to show no benefit to its use, other studies in generally high-risk pregnancies, which included maternal hypertensive disorders, did demonstrate advantages in terms of reduced perinatal mortality and better decision-making. The GDG feels that these

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

findings can be extrapolated to hypertensive pregnancies generally and that this should be included in any ultrasound assessment. Given the lack of good tests that might predict which women would progress to pre-eclampsia and the overall lower rate of pre-eclampsia in late-onset disease, there seems little justification for routine use of any type of ultrasound surveillance at term.

Formal fetal movement counting conferred no benefit in terms of reduced perinatal mortality or interventions in the general population and is not recommended for fetal surveillance in other guidance ('Antenatal care', NICE clinical guideline 62).[1] For amniotic fluid volume, the evidence did not relate specifically to pregnancies complicated by hypertension but the comparison between methods of amniotic fluid assessment favoured the single deepest vertical pocket – the amniotic index resulted in more intervention without clear benefit. Given the general evidence on biophysical profiles, the GDG would see no reason to consider these in women with gestational hypertension.

The overall evidence in favour of antenatal cardiotocography is not encouraging and yet it is probably one of the most commonly performed tests in pregnancy. The GDG recognises that any attempt to withdraw its use would not find widespread support but recommends that its use should be rationalised such that there are clear indications for repeat testing, such as where the woman reports a change in fetal movement or has vaginal bleeding or abdominal pain.

Severe gestational hypertension requires hospital admission and the GDG feels that the level of fetal surveillance should at least initially mimic that for pre-eclampsia (see Chapter 7).

Recommendations relating to fetal monitoring in women with gestational hypertension are presented in Chapter 8.

6.7 Timing of birth

Clinical effectiveness

A multicentre open-label RCT,[126] [EL = 1+] the Hypertension and Pre-eclampsia Intervention Trial (HYPITAT), was conducted in the Netherlands and compared induction of labour (aim within 24 hours) with expectant management in women with gestational hypertension or mild pre-eclampsia ($n = 756$). Women were randomly allocated, using blocked randomisation with a variable block size of 2–8, into an induction of labour group ($n = 377$) or an expectant monitoring group ($n = 379$). Randomisation was stratified by centre (six academic and 32 non-academic hospitals), parity (nulliparous or multiparous) and hypertensive disorder (gestational hypertension or pre-eclampsia). Baseline characteristics of the two groups were similar.

The primary outcome was a composite measure of adverse maternal outcome defined as maternal mortality, maternal morbidity (eclampsia, HELLP syndrome, pulmonary oedema, thrombolytic disease or placental abruption), progression to severe hypertension, or major postpartum haemorrhage. The only adverse maternal outcome was a progression to severe hypertension and this occurred less frequently in women in the induction of labour group (117 (31%) versus 166 (44%); RR 0.71; 95% CI 0.59 to 0.86). No maternal deaths were reported in either group. There was a statistically significantly lower risk of progression to severe disease in the induction of labour group (88 (23%) versus 138 (36%); RR 0.64; 95% CI 0.51 to 0.80) as well as a statistically significantly lower risk of severe hypertension (systolic blood pressure: 55 (15%) versus 88 (23%); RR 0.63; 95% CI 0.46 to 0.86, diastolic blood pressure: 62 (16%) versus 103 (27%); RR 0.61; 95% CI 0.46 to 0.80). There was a trend towards fewer maternal admissions to intensive care in the induction of labour group but the difference was not statistically significant (6 (2%) versus 14 (4%); RR 0.41; 95% CI 0.16 to 1.07).

No neonatal deaths were reported in either group, and there were no statistically significant differences between the two groups in terms of composite adverse neonatal outcome (Apgar score less than 7 at 5 minutes, umbilical artery pH less than 7.05 or admission to NICU), Apgar score less than 7 at 5 minutes, admission to NICU, or duration of stay in neonatal intensive, high or medium care unit). However, umbilical artery pH less than 7.05 occurred statistically significantly less frequently in babies of women in the induction of labour group (9 (2%) versus 19 (5%), RR 0.46; 95% CI 0.21 to 1.00). Babies in the induction of labour group also had

statistically significantly lower birthweights (median 3220 g; interquartile range (IQR) 2429 to 4131 g versus 3490 g; IQR 2570 to 4235 g; CI not reported; $P < 0.0001$), but this was because the babies in the induction of labour group were born at an earlier stage of pregnancy.

There were no statistically significant differences between the two groups in the modes of delivery (spontaneous, vaginal instrumental or caesarean section).

Subgroup analyses were reported for the composite adverse maternal outcome and for caesarean section rates. For women with (mild) pre-eclampsia, there was a statistically significant reduction in the frequency of severe hypertension in the induction of labour group (41 (33%) versus 67 (54%), RR 0.61; 95% CI 0.45 to 0.82). However, for women with gestational hypertension, there was no statistically significant difference in the development of severe hypertension between the two groups (75 (31%) versus 96 (38%); RR 0.81; 95% CI 0.63 to 1.03). There were no statistically significant differences in caesarean section rates between the groups for women with pre-eclampsia (22 (18%) versus 29 (24%); RR 0.76; 95% CI 0.46 to 1.24) or with gestational hypertension (31 (13%) versus 42 (17%); RR 0.76; 95% CI 0.50 to 1.17).

Evidence statement

One RCT[126] [EL = 1+] showed that induction of labour in women with gestational hypertension or mild pre-eclampsia statistically significantly lowered the risks of progression to severe hypertension compared with women who received expectant management. Subgroup analyses showed a statistically significant reduction in the frequency of progression to severe hypertension with induction of labour in women with (mild) pre-eclampsia but not in women with gestational hypertension. No clinically significant differences were reported in neonatal outcomes, nor in mode of delivery (even for the subgroups of women with gestational hypertension and and with mild pre-eclampsia).

Cost effectiveness

A literature search identified no published economic evaluations comparing immediate birth (induction of labour) with expectant management in women with mild or moderate gestational hypertension at term. The two strategies have different resource implications and health consequences for the mother and baby. In view of the lack of published cost-effectiveness evidence, the GDG requested an original health economic analysis to help in the formulation of guideline recommendations. The results of the analysis are summarised here and further details are presented in Appendix I.

Using data from the recently published HYPITAT trial,[126] a decision tree was constructed in Excel™ and TreeAge Pro® to estimate the cost effectiveness of the two strategies (immediate birth and expectant management). The model demonstrated that immediate birth was cost saving compared with expectant management in women with mild or moderate gestational hypertension at term. Immediate birth dominated expectant management, in that it resulted in better maternal outcomes and was less costly compared with expectant management. The mean cost per woman for immediate birth was estimated to be £2,774 compared with £2,990 for expectant management. This resulted in savings of £213 per woman as well as generating 0.04 more QALYs. A probabilistic analysis showed that immediate birth was cost effective all the time (100%). In 99% of 1000 iterations, immediate birth was cost saving. It was shown, using univariate sensitivity analysis, that the base-case results were robust to changes in model assumptions except for changes in the incidence of severe disease.

GDG interpretation of the evidence

The HYPITAT trial[126] combined mild pre-eclampsia (as defined in this guideline) and mild gestational hypertension (defined as diastolic blood pressure of 95 mmHg or higher compared with 90 mmHg or higher in this guideline). Subgroup analyses were reported for the primary outcome (adverse maternal outcome) and for caesarean section rates. The overall maternal benefits reported in the trial were maintained in the subgroup of women with mild pre-eclampsia, and therefore the GDG feels that the study results are sufficient to inform practice for this group of women. The subgroup analysis for gestational hypertension showed a trend to better maternal outcomes (less development of severe hypertension) but the difference was not

statistically significant. Also, women with mild gestational hypertension with blood pressure in the range 90–94 mmHg were not included in the trial.

There appear to be no advantages to immediate birth for women with gestational hypertension, other than the prevention of progression to severe hypertension. Our economic model based on the HYPITAT trial also demonstrated that immediate birth was cost saving when compared with expectant management. This result was driven by the difference in the occurrence of severe disease between the two strategies. Current UK practice and the recommendations made in this guideline focus on antihypertensive treatment to control blood pressure in women with moderate or severe hypertension, and this should precede an offer of early birth. The GDG's view is that the results of the HYPITAT trial are not directly applicable to the UK clinical setting because in the Netherlands gestational hypertension is managed by offering immediate birth without antihypertensive treatment. However, the GDG's view is that if gestational hypertension becomes severe (160/110 mmHg or higher), even with antihypertensive treatment, then the woman should be offered immediate birth after a course of corticosteroids has been administered. The decision on timing of birth should involve consideration of blood pressure and its treatment, potential complications associated with induction of labour, health of the fetus, other obstetric complications, and the woman's preferences. The GDG's view is that senior obstetric involvement is, therefore, required in the decision-making process.

Recommendations

Do not offer birth before 37 weeks to women with gestational hypertension whose blood pressure is lower than 160/110 mmHg, with or without antihypertensive treatment.

For women with gestational hypertension whose blood pressure is lower than 160/110 mmHg after 37 weeks, with or without antihypertensive treatment, timing of birth, and maternal and fetal indications for birth should be agreed between the woman and the senior obstetrician.

Offer birth to women with refractory severe gestational hypertension after a course of corticosteroids (if required) has been completed.

6.8 Postnatal investigation, monitoring and treatment

Clinical effectiveness

A single literature search was conducted for the various postnatal investigations and interventions covered. The population comprised postnatal women who presented with pre-existing hypertensive disorders or new hypertension during their pregnancies. The search identified 1979 references, of which 31 were retrieved. There was no evidence for observations or monitoring.

Frequency of observations or investigations

No evidence was identified in relation to frequency of observations or investigations.

Choice of antihypertensive treatment

Timolol versus methyldopa

An RCT from the UK[127] [EL = 1–] compared the use of timolol and methyldopa in the management of puerperal hypertension. Untreated postpartum women with diastolic blood pressure in the range 95–105 mmHg were randomly allocated to receive either timolol ($n = 40$; 5 mg orally, three times a day) or methyldopa ($n = 40$; 250 mg orally, three times a day). In both cases, the dose was doubled every 24 hours twice if diastolic blood pressure was above 95 mmHg. Antenatally, 46 of the 80 women had received drug treatment for hypertension and another 14 had had mild hypertension (less than 95 mmHg) that had not required treatment. The remaining 20 women had not been hypertensive before delivery.

There was no difference in the need for additional antihypertensive therapy between the two groups (3/40 versus 1/40; RR 3.00; 95% CI 0.33 to 27.63). There was also no statistically

significant difference in the number of those who had their medications changed owing to maternal side effects (1/40 versus 2/40; RR 0.50; 95% CI 0.05 to 5.30).

Antihypertensive drugs and breastfeeding

The use of antihypertensive drugs during breastfeeding is discussed in Chapter 11.

GDG interpretation of the evidence

There is little evidence to support the use of basic observations in the postnatal period and these should be largely clinically driven in type and frequency. Peak blood pressure in the postnatal period occurs 3–5 days after birth and it would be sensible for blood pressure to be assessed at this time, whatever the birth or postnatal setting. Similarly, blood pressure monitoring would be sensible if treatment were altered.

Target blood pressures will be those used in long-term treatment of hypertension.

There is no evidence in relation to the effectiveness of antihypertensive drugs in the postnatal period for women with gestational hypertension. The GDG's view is, therefore, that antenatal antihypertensive treatment should continue. Methyldopa has a well-recognised association with clinical depression and should be avoided in the postnatal period, where feasible.

Women with gestational hypertension who have taken antihypertensive treatment should have their blood pressure monitored and treatment reduced and, if possible, stopped as blood pressure falls. The GDG is aware that a significant minority of women with gestational hypertension will, in fact, have undiagnosed chronic hypertension. The GDG considers that an individualised care plan should be established before transfer to community care. The GDG's view is that women with gestational hypertension should be offered a formal medical review at the postnatal review (6–8 weeks after the birth). Who provides this review will depend on local circumstances and the level of expertise of individual healthcare professionals, and so the GDG was not able to be prescriptive on this point. However, the woman's care plan should document who will provide follow-up care, including medical review if required. The medical review should include measurement of blood pressure, urine testing and review of antihypertensive drugs.

The GDG's view is that women who have had gestational hypertension and who still need antihypertensive treatment at the postnatal review (6–8 weeks after the birth) should be offered a specialist assessment of their hypertension. Chronic hypertension in women who had gestational hypertension should be diagnosed and managed in accordance with 'Hypertension', NICE clinical guideline 34.[3]

Recommendations

In women with gestational hypertension who have given birth, measure blood pressure:

- daily for the first 2 days after birth
- at least once between day 3 and day 5 after birth
- as clinically indicated if antihypertensive treatment is changed after birth.

In women with gestational hypertension who have given birth:

- continue use of antenatal antihypertensive treatment
- consider reducing antihypertensive treatment if their blood pressure falls below 140/90 mmHg
- reduce antihypertensive treatment if their blood pressure falls below 130/80 mmHg.

If a woman has taken methyldopa† to treat gestational hypertension, stop within 2 days of birth.

For women with gestational hypertension who did not take antihypertensive treatment and have given birth, start antihypertensive treatment if their blood pressure is higher than 149/99 mmHg.

Write a care plan for women with gestational hypertension who have given birth and are being transferred to community care that includes all of the following:

- who will provide follow-up care, including medical review if needed
- frequency of blood pressure monitoring needed
- thresholds for reducing or stopping treatment
- indications for referral to primary care for blood pressure review.

Offer women who have had gestational hypertension and remain on antihypertensive treatment 2 weeks after transfer to community care, a medical review.

Offer women who have had gestational hypertension a medical review at the postnatal review (6–8 weeks after the birth).

Offer women who have had gestational hypertension and who still need antihypertensive treatment at the postnatal review (6–8 weeks after the birth) a specialist assessment of their hypertension.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

7 Management of pregnancy with pre-eclampsia

7.1 Introduction

The risk of maternal and perinatal mortality and morbidity is increased once a diagnosis of pre-eclampsia is made. Pre-eclampsia is a multisystem disease and the level of hypertension is not the only consideration. Measurement of biochemical and haematological parameters may be useful in determining the systems involved and in establishing the risk of serious adverse outcomes in the women or baby.

Clinical management is often determined by drawing a balance between maternal and fetal considerations. For example, the timing of birth depends on the mother's condition and the risk to the baby of intrauterine death or, if born, neonatal death or morbidity as a result of prematurity.

This section examines the clinical care of women before transfer to labour ward and after discharge from labour ward.

7.2 Frequency of blood pressure measurement

No studies could be identified regarding the frequency with which blood pressure should be measured for any of the populations.

7.3 Assessment of proteinuria

Clinical effectiveness

One systematic review investigated the precise estimates of likelihood ratios (LRs) of adverse maternal and fetal complications for various cut-off levels of proteinuria in women with pre-eclampsia.[128] [EL = Ib] The review included 16 diagnostic studies ($n = 6749$ women with pre-eclampsia) looking at the use of only urine dipstick (five studies), only laboratory method (eight studies), either dipstick or laboratory method (two studies) or only the protein : creatinine ratio (one study) to assess maternal or fetal complications. Studies were considered to be of good quality if they used prospective design (five studies), consecutive enrolment (six studies) and full verification of the test result with reference standard (16 studies) and had adequate test description (ten studies). It is not clear which studies (if any) fulfilled all the criteria. Case–control studies were excluded and there were no language restrictions.

All five studies ($n = 7066$) found there was an increased likelihood of stillbirth with proteinuria, and a reduced likelihood of stillbirth in the absence of proteinuria (5 g/24 hour: three studies, $n = 546$; LR+ 2.0 (95% CI 1.5 to 2.7); LR– 0.53 (95% CI 0.27 to 1.0); 1+: one study, $n = 3260$; LR+ 1.3 (95% CI 1.2 to 1.4); LR– 0.69 (95% CI 0.59 to 0.82); 3+: one study, $n = 3260$; LR+ 2.3 (95% CI 1.9 to 2.7); LR– 0.76 (95% CI 0.70 to 0.84)). Four studies ($n = 888$) out of seven studies ($n = 1180$) had statistically significant findings that there was an increased likelihood of an SGA baby in the presence of proteinuria and a reduced likelihood in the absence of proteinuria (2+: one study, $n = 307$; LR+ 1.3 (95% CI 1.1 to 1.5); LR– 0.45

(95% CI 0.21 to 0.96); 3+: two studies, $n = 386$; LR+ 1.6 (95% CI 1.1 to 2.3); LR– 0.75 (95% CI 0.59 to 0.96); 0.5 g/24 hour: one study, $n = 195$; LR+ 1.7 (95% CI 1.1 to 2.7); LR– 0.73 (95% CI 0.52 to 1.0)). No statistically significant LRs for SGA were found at a proteinuria cut-off of 1+ (one study, $n = 87$), 300 mg/24 hour (one study, $n = 195$) or 5 g/24 hour (one study, $n = 107$). Three studies ($n = 525$) out of six studies ($n = 952$) found an increased likelihood of NICU admission in the presence of proteinuria and a reduced likelihood of NICU admission in the absence of proteinuria (5 g/24 hour: two studies, $n = 316$; LR+ 1.5 (95% CI 1.0 to 2.0); LR– 0.78 (95% CI 0.64 to 0.95); 10 g/24 hour: one study, $n = 209$; LR+ 5.6 (95% CI 1.8 to 17.4); LR– 0.77 (95% CI 0.69 to 0.87)). No statistically significant LRs for NICU admission were found for cut-offs of 1+ (one study, $n = 87$) or increase by 2 g/24 hour (one study, $n = 340$). One study ($n = 209$) out of three studies ($n = 492$) found a statistically significant increase in likelihood of eclampsia in the presence of proteinuria (10 g/24 hour: LR+ 2.7, 95% CI 1.1 to 6.2). However, at the same level of proteinuria there was no reduction in likelihood of eclampsia in the absence of proteinuria, and no statistically significant LRs were found at a cut-off of 5 g/24 hour (one study, $n = 209$) or increase by 2 g/24 hour (one study, $n = 74$). One study ($n = 321$) out of three studies ($n = 1079$) found a statistically significant increase in likelihood for perinatal death in the presence of proteinuria (500 mg/mmol: LR+ 5.3, 95% CI 1.3 to 22.1). However, no statistically significant reduction in likelihood was found at the same cut-off, and no statistically significant LRs were found at a cut-off of 1 g/litre (one study, $n = 379$) or 2 g/litre (one study, $n = 379$). There were no statistically significant findings for the likelihood of placental abruption (three studies, $n = 247$), HELLP syndrome (four studies, $n = 558$) or neonatal death (five studies, $n = 698$) in the presence or absence of proteinuria. The study concluded that proteinuria is a poor predictor of maternal or fetal complications in women with pre-eclampsia.

Evidence statement

One systematic review [EL = Ib] looked at using proteinuria to predict maternal and fetal outcomes in women with pre-eclampsia. Low LRs for stillbirth and SGA were found in the majority of studies and for NICU admission in half of the studies but LRs were in the range of values regarded as of little predictive use. One study reported a statistically significant but weak positive LR for eclampsia and another for perinatal death, but no other statistically significant results for eclampsia or perinatal death were found.

GDG interpretation of the evidence

The extensive systematic review showed no strong evidence linking the level of proteinuria with adverse outcome. Positive LRs are generally between 1 and 2, which are considered of little value as predictive tests. The evidence was also drawn from a variety of studies using different cut-off levels for proteinuria. The GDG's view is that once the diagnosis of significant proteinuria has been made there is little benefit from repeating the analysis.

7.4 Biochemical tests

Uric acid

Clinical effectiveness

A systematic review of 18 primary articles, comprising 41 studies and 3913 women with pre-eclampsia, was conducted to evaluate the effectiveness of maternal serum uric acid in predicting maternal and fetal outcome.[129] [EL = III] Heterogeneity was present between the individual studies with regard to populations, definition of pre-eclampsia, test thresholds, frequency of testing, the interval between the test and outcome, and reference standards. Therefore, a random effects model was used for pooling the individual studies.

The overall pooled positive and negative LRs for serum uric acid (three studies, $n = 634$) for predicting eclampsia, using the threshold of 350 micromol/litre, were 2.1 (95% CI 1.4 to 3.5) and 0.38 (95% CI 0.18 to 0.81), respectively.

The pooled LRs for predicting severe hypertension were 1.7 (95% CI 1.3 to 2.2) and 0.49 (95% CI 0.38 to 0.64) including six studies and 1583 women. Only one study ($n = 194$) had HELLP syndrome as an outcome. The positive and negative LRs for 450 micromol/litre serum uric acid were 1.6 (95% CI 0.73 to 3.3) and 0.90 (95% 0.56 to 1.4), respectively, and 1.9 (95% CI 0.85 to 4.2) and 0.92 (95% 0.81 to 1.0), respectively, for a threshold of 540 micromol/litre.

Fetal outcomes included SGA, stillbirth and neonatal death. Pooled positive and negative LRs were 1.3 (95% CI 1.1 to 1.7) and 0.60 (95% CI 0.43 to 0.83), respectively, for predicting the birth of an SGA infant. Five studies ($n = 1219$) were included for these pooled estimates. For predicting stillbirth and neonatal death, four studies ($n = 1040$) were included in the meta-analysis and the pooled positive and negative LRs were 1.5 (95% CI 0.91 to 2.6) and 0.51 (95% CI 0.20 to 1.3), respectively. The studies included for intrauterine death could not be combined because of the use of different thresholds and so were reported individually. One study ($n = 43$) used a threshold of 300 micromol/litre and had positive and negative LRs of 2.7 (95% CI 0.71 to 9.8) and 0.13 (95% CI 0.01 to 2.4), respectively. Another study ($n = 200$) used a threshold of 330 micromol/litre and had positive and negative LRs of 2.8 (95% CI 0.42 to 18.3) and 0.28 (95% CI 0.01 to 5.9), respectively. The study using a threshold of 350 micromol/litre ($n = 103$) had positive and negative LRs of 2.1 (95% CI 0.89 to 5.1) and 0.07 (95% CI 0.01 to 1.3), respectively, and the study using a threshold of 520 micromol/litre ($n = 229$) positive and negative LRs of 1.5 (95% CI 0.40 to 5.3) and 0.93 (95% CI 0.46 to 1.9), respectively. Subgroup analysis was undertaken for various severity levels of pre-eclampsia and various thresholds. The results of the subgroup analyses did not differ essentially from the overall results.

Evidence statement

One systematic review evaluated the effectiveness of serum uric acid in predicting maternal and neonatal outcome. The pooled LRs showed serum uric acid to be a weak predictor for eclampsia (LR+ = 2.1 and LR− = 0.38) and for severe hypertension (LR+ = 2.4 and LR− = 0.39). Two individual studies concerning the prediction of HELLP syndrome had non-statistically significant LRs. Serum uric acid seems to be weakly effective in predicting SGA babies (pooled LR+ = 1.3 and LR− = 0.60) but not for predicting stillbirth or neonatal death – the pooled LRs for stillbirth and neonatal death were not statistically significant. Four individual studies on serum uric acid for predicting intrauterine death were all not statistically significant.

Renal function tests, platelets and liver function

Clinical effectiveness

A retrospective observational study, including 111 women with pre-eclampsia, was conducted in Sweden to identify risk factors predicting maternal or fetal complications.[130] [EL = 2+] Of the included women, 70 had mild pre-eclampsia, 41 had severe pre-eclampsia and none had a history of chronic hypertension. Three women had type 1 diabetes. Pre-eclampsia was defined as blood pressure of 140/90 mmHg or higher together with albuminuria of at least 300 mg/24 hours after 20 weeks of gestation. Severe pre-eclampsia was defined according to the American College of Obstetricians and Gynecologists (ACOG). Blood was sampled at admission and haemoglobin, platelets, liver enzymes, uric acid and creatinine were analysed. When the analysis indicated HELLP syndrome, lactate dehydrogenase (LDH) was analysed. Blood pressure was checked four times a day. Twenty-four-hour urinary albumin excretion was measured daily from admission. Plasma sampling was repeated daily to every third day, depending on the severity of pre-eclampsia. Unadjusted ORs originating from univariate analysis were reported. Variables with P values below 0.140 in the univariate analysis were entered into a multivariate model that gave adjusted ORs. The ORs for each variable were related to a unit change for that variable, for example a blood pressure change of 1 mmHg and a change of 1 g for 24-hour albumin excretion. One unit change in alanine aminotansferase (ALT) represented a change of 0.1 microkat/litre in LDH. Maternal complications were defined as eclampsia, placental abruption, oliguria (urine production less than 600 ml/24 hours) and HELLP syndrome (LDH more than 8 microkat/litre, ALT more than 0.70 microkat/litre and platelet count less than 150×10^9/litre).

Significant ORs for maternal complications in the univariate analysis were systolic blood pressure (OR 1.05; 95% CI 1.01 to 1.09) and diastolic blood pressure (OR 1.15; 95% CI 1.06 to 1.26). Significant albumin excretion had a borderline statistically significant OR (OR 1.31; 95% CI 1.00 to 1.72). Liver enzymes, platelets and haemoglobin were excluded when predictors for maternal complications were evaluated because nearly half of the women with maternal complications had HELLP syndrome.

Odds ratios for creatinine, uric acid and albumin were not statistically significant. After adjustment for confounding factors (found to be associated with the outcome in the univariate analysis), only the OR for diastolic blood pressure (OR 1.13; 95% CI 1.01 to 1.25) remained statistically significant. None of the following variables was predictive for giving birth to an SGA infant: creatinine, uric acid, albumin, haemoglobin, platelets, ALT, albumin excretion, and systolic and diastolic blood pressure. None of these associations became statistically significant after adjustment for confounders. Variables predictive for admittance to the NICU were ALT (OR 1.13; 95% CI 1.01 to 1.26), systolic blood pressure (OR 1.05; 95% CI 1.02 to 1.08) and diastolic blood pressure (OR 1.08; 95% CI 1.02 to 1.13). These associations were statistically significant in the univariate analysis but disappeared after adjustment for confounding variables. Creatinine, uric acid, albumin, haemoglobin, platelets and albumin excretion were not statistically significantly associated with admittance to the NICU.

A cohort study was conducted in Canada, New Zealand, the UK and Australia.[131] [EL = 2+] It looked at 737 women with hypertension and proteinuria ($n = 464$), hypertension and hyperuricaemia ($n = 116$) and HELLP syndrome without hypertension or proteinuria ($n = 30$) or superimposed pre-eclampsia ($n = 127$). The study compared factors measured at presentation of illness with adverse maternal and perinatal outcomes. Not all women had each factor recorded, and probability values for adverse outcomes were not analysed if data were only available for less than 80% of the study group.

There was a statistically significant association between adverse maternal and perinatal outcomes and platelets below 100×10^9/litre (53 of 735 women; $P = 0.001$ and $P = 0.013$, respectively). There was a statistically significant association between adverse maternal outcomes, but not adverse perinatal outcomes, and elevated liver enzymes (352 of 737 women; $P < 0.001$ and $P = 0.868$, respectively), creatinine greater than 110 micromol/litre (18 of 734 women; $P < 0.001$ and $P = 1.000$, respectively), increased aspartate aminotransferase (AST) and/or ALT (183 of 737 women; $P = 0.006$ and $P = 0.085$, respectively) and increased LDH or microangiopathic haemolytic anaemia (292 of 698 women; $P = 0.001$ and $P = 0.374$, respectively).

There was no statistically significant association between adverse maternal or perinatal outcomes and serum albumin less than 18 g/litre (11 of 652 women; $P = 0.328$ and $P = 0.438$, respectively) or proteinuria of greater than or equal to 2+ (445 of 726 women; $P = 0.609$ and $P = 0.060$, respectively).

Evidence statement

One study investigated factors associated with maternal and fetal complications among women with pre-eclampsia. Out of the investigated factors only systolic and diastolic blood pressure and albumin excretion were statistically significantly associated with maternal complications in the univariate analysis. After adjustment, ORs remained statistically significant only for diastolic blood pressure (OR 1.13; 95% CI 1.01 to 1.25). Creatinine, uric acid and albumin did not prove to be statistically significantly associated with maternal outcomes. None of the nine factors investigated (creatinine, uric acid, albumin, haemoglobin, platelets, ALT, albumin excretion and systolic and diastolic blood pressure) were associated with giving birth to an SGA infant. Univariate analysis showed that systolic and diastolic blood pressure and ALT were statistically significantly associated with referral to NICU.

A retrospective cohort study showed an association between a platelet count less than 100×10^9/litre, elevated transaminases and creatinine more than 110 micromol/litre and serious adverse maternal outcomes, but no relationship with perinatal outcomes.

Coagulation

None of the retrieved evidence was considered to be suitable to answer the question.

GDG interpretation of the evidence

There are no data to inform the frequency of blood pressure measuring. The consensus of the GDG is that the frequency of monitoring blood pressure depends on the severity of hypertension and the presence of risk factors.

The GDG believes that there is no evidence to support a change from the safe routine practice of blood pressure recordings at least four times a day in women with mild or moderate new-onset hypertension and proteinuria while an inpatient.

The risk of CVA is increased in severe hypertension and blood pressure should be recorded more frequently to detect rises in blood pressure and responses to therapy.

The only positive findings from a systematic review examining the degree of proteinuria and maternal and perinatal outcomes were the weak association between proteinuria more than 5 g/24 hours and stillbirth, admission to NICU and SGA. Likelihood ratios were small. The degree of proteinuria does not appear to be related to maternal outcomes. Overall, the GDG considers that the evidence does not support repeated measures of urinary protein once significant proteinuria is established.

The GDG feels that there is sufficient evidence that platelet count, serum creatinine, and transaminases are useful indicators for progression to more severe disease in women with pre-eclampsia. Rising serum uric acid is associated with severe pre-eclampsia but was not shown to be of additional value to the tests listed above. Available evidence shows that tests of coagulation are not helpful where the platelet count is above 100×10^9/litre.

7.5 Treatment of hypertension

Clinical effectiveness

The data are summarised in Table 7.1 (women with pre-eclampsia) and Table 6.2 (mixed populations) and the details of the studies are presented below.

Alpha- and beta-blockers

One RCT investigated the effectiveness of labetalol versus no treatment.[132] [EL = 1+] Statistically significantly fewer women developed severe hypertension when they were treated with labetalol compared with no treatment (RR 0.36; 95% CI 0.14 to 0.97). No statistically significant differences between the labetalol group and the control group were reported for any other maternal or fetal outcomes considered in the study.

Methyldopa

Two trials investigated the effectiveness of methyldopa: one study[133] [EL = 1–] compared it with no treatment and one with the calcium-channel blocker isradipine.[134] [EL = 1–]

In addition, some of the mixed trials presented in Chapter 6 included women with pre-eclampsia.

An RCT conducted in Sudan compared methyldopa with no drug treatment.[133] [EL = 1–] Women were included if they had a singleton pregnancy at between 28 and 36 weeks of gestation, a diastolic blood pressure between 90 and 109 mmHg in two readings 6 hours apart, and 2+ albumin on dipstick or more. The included women ($n = 74$) were randomly allocated to two groups: one group received methyldopa ($n = 34$) while the other received no drug treatment but were admitted to hospital for bed rest ($n = 36$). Initially, 750 mg/day methyldopa was given and gradually increased to a maximum of 4 g/day. In cases of imminent eclampsia, pregnancies were terminated regardless of gestational age. The study did not give any information on randomisation, allocation concealment or blinding.

Table 7.1a Reported results of treatment for women with pre-eclampsia – intervention compared with no treatment (reported as RRs or ORs with 95% CIs)

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Labetalol versus no treatment (all study participants were inpatients)									
Sibai *et al.* (1987)[132] [EL = 1+] USA	5/92 versus 14/94 RR 0.36 (0.14 to 0.97)	10/92 versus 6/94 RR 1.70 (0.65 to 4.49)	0/92 versus 0/94 not estimable	–	–	1/94 versus 0/97 RR 3.09 (0.13 to 75.03)	18/94 versus 9/97 RR 2.06 (0.98 to 4.36)	–	38/94 versus 40/97 RR 0.98 (0.70 to 1.38)
Methyldopa versus no treatment (all study participants were inpatients)									
Elhassan *et al.* (2002)[133] [EL = 1−] Sudan	–	3/34 versus 18/36 RR 0.18 (0.06 to 0.55)[a]	–	0/34 versus 0/36 not estimable	–	4/34 versus 6/36 RR 0.71 (0.22 to 2.29)	–	–	11/34 versus 7/36 RR 1.67 (0.73 to 3.80)[b]

HDU = high-dependency unit; HELLP = haemolysis, elevated liver enzymes and low platelet count; ICU = intensive care unit; NICU = neonatal intensive care unit; SGA = small for gestational age

[a] Severe pre-eclampsia with proteinuria > 5 g/24 hours

[b] Referral to a paediatrician

Table 7.1b Reported results of treatment for women with pre-eclampsia – comparison of two interventions (reported as RRs or ORs with 95% CIs)

Study	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP syndrome	Maternal death	Admission to HDU/ICU	Perinatal mortality	SGA	Preterm birth	Admission to NICU
Methyldopa versus isradipine (all study participants were inpatients)									
Montan *et al.* (1996)[134] [EL = 1−][a] Singapore	–	–	–	–	–	–	–	–	–
Nifedipine and bed rest versus bed rest alone									
Sibai *et al.* (1992)[135] [EL = 1+] USA	9/98 versus 18/99 RR 0.51 (0.24 to 1.07)[b]	16/98 versus 10/99 RR 1.62 (0.77 to 3.39)	4/98 versus 2/99 RR 2.02 (0.38 to 10.78)[c]	–	–	0/99 versus 0/101 not estimable	15/99 versus 13/101 RR 1.18 (0.59 to 2.35)[d]	49/99 versus 41/101 RR 1.23 (0.88 to 1.70)	30/99 versus 21/101 RR 1.46 (0.90 to 2.36)

HDU = high-dependency unit; HELLP = haemolysis, elevated liver enzymes and low platelet count; ICU = intensive care unit; NICU = neonatal intensive care unit; SGA = small for gestational age

[a] Reported outcomes are summarised in the text

[b] Reported as statistically significant by the study authors

[c] Reported outcome was HELLP syndrome

[d] Reported outcome was birthweight < 10th percentile

Converting the reported incidence figures into relative risks showed that women receiving methyldopa were considerably less likely to develop severe pre-eclampsia compared with women on bed rest only (RR 0.18; 95% CI 0.06 to 0.55). A similar result, but not statistically significant, was found for the incidence of imminent eclampsia (RR 0.32; 95% CI 0.10 to 1.06).

There were no statistically significant differences between the two groups for maternal death, perinatal death, referral of the baby to a paediatrician, gestational age at delivery, birthweight or Apgar score less than 7 at 5 minutes.

A very small low-quality RCT was conducted in Singapore comparing methyldopa with isradipine.[134] [EL = 1−] Women with pre-eclampsia ($n = 27$) received either 250 mg methyldopa three times a day ($n = 10$) or 2.5 mg oral slow-release isradipine twice a day ($n = 11$). Six women were excluded after randomisation. No further information on randomisation was given and none of the women was blinded. No statistical tests were carried out to compare the two treatment groups. The mean birthweight was 2648 g in the methyldopa group (SD 510 g) and 2866 g (SD 428 g) in the isradipine group (two-tailed P calculated by t-test from the reported means and SD: $P = 0.30$). One woman from each treatment group had a caesarean section. One baby of a mother receiving methyldopa, and no baby of mothers receiving isradipine, had an Apgar score less than 7 at 5 minutes.

Calcium-channel blockers

A well-conducted RCT in the USA compared nifedipine in combination with bed rest with bed rest alone.[135] [EL = 1+] Women were included if they had mild pre-eclampsia at 26–36 weeks of gestation. All included women had persistent elevations of blood pressure (systolic between 140 and 160 mmHg and/or diastolic between 90 and 110 mmHg) 24 hours after hospitalisation and proteinuria defined as either more than 300 mg/24 hours or at least 2+ proteinuria on dipsticks and/or elevated uric acid levels (lat least 6 mg/dl) at the time of entry to the study. Women with associated medical and obstetric complications other than pre-eclampsia and women with fetal compromise (suspected abnormal fetal growth by ultrasonography and/or abnormal fetal testing) were excluded from the study. One hundred women received bed rest in combination with 40 mg/day nifedipine, which was increased every 2 to 3 days as needed to a maximum of 120 mg/day to keep systolic blood pressure below 140 mmHg and diastolic blood pressure below 90 mmHg. The comparison group consisted of 100 women receiving bed rest alone. No statistically significant results were found in this study.

Evidence statement

Four studies were included for women with pre-eclampsia. No suitable evidence was identified for diuretics, antiplatelet agents, rest or bed rest. A small trial of low quality[133] [EL = 1−] found methyldopa to be effective in preventing severe pre-eclampsia compared with placebo. Another small trial[134] of low quality [EL = 1−] compared methyldopa with isradipine but did not achieve any statistically significant results. One RCT[132] [EL = 1+] found that labetalol reduced progression to severe hypertension compared with no treatment. A well-conducted trial[135] [EL = 1+] found nifedipine combined with bed rest to not improve maternal or fetal outcomes compared with bed rest alone. This study did not show any statistically significant results.

GDG interpretation of the evidence

Treatment with antihypertensive agents

Limited good-quality evidence is available in relation to treatment of pre-eclampsia. There is no evidence that blood pressure lowering treatment for women who have pre-eclampsia with mild or moderate hypertension improves pregnancy outcomes compared with starting treatment once severe hypertension has developed.

However, the evidence base is not large enough to know whether antihypertensive treatment prevents uncommon outcomes such as maternal CVA or placental abruption. There is some evidence about the appropriate level of blood pressure to be aimed for by treatment (see Section 4.4.2). This suggests increased risks of severe hypertension with less tight control (diastolic blood pressure above 90 mmHg or 100 mmHg) with no clear evidence of an effect on fetal growth.

There is some evidence to show that labetalol reduces the risk of progression to severe hypertension. There was little evidence on the use of calcium-channel blockers.

The GDG considered the suggested association between maternal treatment with beta-blockers and IUGR and neonatal beta-blockade and their consensus was that the reported adverse effects were likely to be dose related and as a result of excessive lowering of blood pressure.

Labetalol appears to be as effective and safe as other antihypertensive agents for managing pre-eclampsia and, as it is licensed for use in pregnancy, the GDG's view is that labetalol should be used as first-line treatment in this group of women. All NICE clinical guidelines assume that prescribers will use a drug's SPC to inform decisions made with individual patients. The GDG's view is that a specific recommendation should be included in this guideline to highlight alternatives to labetalol, including methyldopa and nifedipine, to be offered after considering side-effect profiles for the woman, fetus and newborn baby. In making this recommendation, the GDG noted concern over the possibility of reduced effectiveness of labetalol in women of Afro-Caribbean origin who do not respond well to beta-blockers. Although this effect is recognised outside pregnancy, and the GDG was not aware of any evidence that of it being repeated in pregnancy, the recommendation to consider alternative antihypertensive treatment covers this group of women, as well as those for whom labetalol is contraindicated (for example, women with asthma).

Recommendations

Assess women with pre-eclampsia at each consultation. Assessment should be performed by a healthcare professional trained in the management of hypertensive disorders of pregnancy.

Offer women with pre-eclampsia an integrated package of care covering admission to hospital, treatment, measurement of blood pressure, testing for proteinuria and blood tests as indicated in the table below.

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110 mmHg or higher)
Admit to hospital	Yes	Yes	Yes
Treat	No	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep: • diastolic blood pressure between 80–100 mmHg • systolic blood pressure less than 150 mmHg
Measure blood pressure	At least four times a day	At least four times a day	More than four times a day, depending on clinical circumstances
Test for proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria
Blood tests	Monitor using the following tests twice a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin	Monitor using the following tests three times a week: kidney function, electrolytes, full blood count, transaminases, bilirubin

Only offer women with pre-eclampsia antihypertensive treatment other than labetalol after considering side-effect profiles for the woman, fetus and newborn baby. Alternatives include methyldopa† and nifedipine.†

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

7.6 Fetal monitoring

Clinical effectiveness

The main evidence is presented in Chapter 8. Only computerised cardiotocography is studied specifically in severe pre-eclampsia and is presented here.

Routine versus computerised cardiotocography in severe pre-eclampsia

One RCT from South Africa compared the use of computerised cardiotocography with routine cardiotocography in monitoring fetal heart rate of women with severe early-onset pre-eclampsia (gestational age 28–34 weeks) whose pregnancies were managed expectantly.[136] [EL = 1+] The study included 59 women who were allocated by random numbers generated by computer and enclosed in successively numbered sealed opaque envelopes into either the computerised cardiotocography group ($n = 29$) or the routine cardiotocography group ($n = 30$). Women at 28–31 weeks were randomised separately from the group at 32–34 weeks to ensure equal distribution of gestational age in the two groups. During labour, all fetal heart-rate monitoring was done with a computerised monitor and visually assessed.

The study showed no statistically significant differences in perinatal loss (four of 29 versus one of 30: RR 4.13; 95% CI 0.49 to 34.86), perinatal morbidity (13 of 29 versus 14 of 30: RR 0.96; 95% CI 0.55 to 1.68) or admission to NICU (nine of 29 versus nine of 30: RR 1.03; 95% CI 0.48 to 2.23) between the two groups. There were also no statistically significant differences in caesarean sections or Apgar score less than 7 at 5 minutes. Standard deviation for gestation, weight, days gained before delivery, duration of stay at NICU and duration of recordings were not reported.

Evidence statement

One small RCT [EL = 1+] showed no difference between the uses of computerised and routine cardiotocography in women with severe pre-eclampsia in terms of perinatal loss, perinatal morbidity or admission to NICU.

GDG interpretation of the evidence

There are no studies that examine fetal surveillance in a population that only includes women with pre-eclampsia and therefore inference on surveillance must be made from general studies of high-risk pregnancies (see Section 6.6).

The single study comparing computerised with conventional cardiotocography did not demonstrate differences.

Recommendations relating to fetal monitoring in women with pre-eclampsia are presented in Chapter 8.

7.7 Timing of birth

Clinical effectiveness

Immediate birth versus expectant management

Two high-quality RCTs[137;138] [EL = 1++ and EL = 1+] investigated whether early delivery or expectant management of severe pre-eclampsia in pregnancies at up to 34 weeks of gestation was more beneficial to maternal and neonatal outcome. In both trials, women had a 24–48 hour period of stabilisation during which they were given steroids to accelerate fetal lung maturity, magnesium sulphate to prevent convulsions and antihypertensives to lower blood pressure. If they continued to meet the eligibility criteria at the end of this period they were then randomised. In both studies, women in the expectant management group were delivered when they reached 34 weeks. Earlier delivery in this group was implemented if the maternal or fetal condition deteriorated.

The larger of these two RCTs was conducted in the USA and involved 95 women at 28–32 weeks with severe pre-eclampsia (systolic blood pressure 160 mmHg or higher or diastolic blood

pressure 110 mmHg or higher, and with proteinuria above 500 mg/24 hours) and elevated serum uric acid levels (more than 5 mg/dl).[137] [EL = 1++] Women with co-existing medical problems were excluded. Women were randomly assigned by computer-generated random numbers to early delivery or expectant management. At the start of the study, the mean age of participants (22 ± 4 years early delivery; 23 ± 6 years expectant management; *P* = NS) and the mean blood pressure (170/110 ± 10/5 mmHg early delivery; 172/112 ± 9/4 mmHg expectant management; *P* = NS) were similar between the two groups. women in the early delivery group (*n* = 46) were prepared for delivery, either by caesarean section or induction, 48 hours after glucocorticoids were administered. Women in the expectant management group (*n* = 49) were managed with bed rest, oral antihypertensives and intensive antenatal fetal testing. Gestational age at delivery was statistically significantly different between the two groups (early delivery 30.8 ± 1.7 weeks; expectant management 32.9 ± 1.5 weeks; $P < 0.0001$). In comparison with the expectant management group, the early delivery group had statistically significantly higher number of neonates admitted to NICU (RR 1.32; 95% CI 1.13 to 1.55), higher mean duration of stay in these units (36.6 ± 17.4 hours versus 20.2 ± 14.0 hours; *P* = 0.0001) and higher frequency of respiratory distress syndrome (RR 2.23; 95% CI 1.23 to 4.04), but early delivery was also associated with reduced risk of SGA babies (RR 0.35; 95% CI 0.14 to 0.90). Incidence rates for placental abruption and HELLP syndrome were similar in the two groups and no eclampsia or perinatal death was reported in either group.

The other RCT was conducted in South Africa.[138] [EL = 1+] It included 38 women at 28–34 weeks with severe pre-eclampsia who were randomly assigned to early delivery (*n* = 20) or expectant management (*n* = 18). The process of randomisation was not described adequately. There was no difference between the mean age of participants (23 ± 5 years early delivery; 23 ± 3 years expectant management; *P* = NS) or the mean blood pressure at the time of entry to the study (159/107 ± 18/8 mmHg early delivery; 159/108 ± 19/11 mmHg expectant management; *P* = NS). Gestational age at delivery was statistically significantly different between the two groups (early delivery 211 ± 15 days; expectant management 223 ± 13 days; $P < 0.05$). Expectant management was not associated with an increase in maternal complications (caesarean section or placental abruption), nor was it associated with an increase in individual neonatal complications (death, necrotising enterocolitis, pneumothorax, hyaline membrane disease). However, it reduced the number of overall neonatal complications (RR 2.25; 95% CI 1.12 to 4.53).

Meta-analyses of the evidence presented in these two RCTs were performed for the guideline. Neonates in the early delivery group showed increased frequency of hyaline membrane disease (two RCTs, *n* = 133; RR 2.30; 95% CI 1.39 to 3.81) and necrotising enterocolitis (two RCTs, *n* = 133; RR 5.54; 95% CI 1.04 to 29.56) than those in the expectant management group, but no statistically significant difference was observed for stillbirth or death after delivery (two RCTs, *n* = 133; RR 1.50; 95% CI 0.42 to 5.41). Meta-analysis of maternal complications (placental abruption and caesarean section) showed no statistically significant differences between the two groups. Other outcomes were reported in only one of the two studies.

One multicentre open-label RCT,[126] [EL = 1+] the HYPITAT trial, compared immediate birth with expectant management in women with mild pre-eclampsia after 36 weeks. The evidence from this trial is presented in Section 6.7.

Effect of IUGR

A multicentre RCT, the Growth Restriction Intervention Trial (GRIT) was undertaken in 13 European countries, including the UK, between 1993 and 2001.[139] [EL = 1+] The study assessed the effect of immediate delivery compared with delayed delivery in (singleton and multiple) pregnancies at between 24 and 36 weeks. The main aim was to assess the level of equipoise between obstetricians in the timing of delivery when there was evidence of potential fetal compromise. There were 273 women in the immediate delivery group and 274 in the delayed delivery group; the incidence of hypertension was 46% and 40%, respectively. Outcomes for the hypertensive cases were not reported separately. Overall, perinatal loss was similar between the groups (10% and 9%, respectively), and there were two stillbirths in the immediate delivery group and nine in the delayed delivery group, but 23 neonatal deaths in the immediate delivery group and 12 in the delayed delivery group.

A second study followed up the GRIT trial after 2 years.[140] [EL = 1+] There were 290 babies in the immediate delivery group and 283 in the delayed delivery group; death or disability occurred in 55 and 44 babies, respectively (OR 1.1; 95% CI 0.7 to 1.8). Most of the observed disability occurred in babies born before 31 weeks (13% immediate delivery versus 5% delayed delivery; *P* = NS).

A retrospective cohort study conducted in Canada assessed morbidity and mortality rates for the woman and fetus in severe pre-eclampsia when the pregnancy was managed expectantly.[141] [EL = 2+] Women whose condition was too unstable and who required delivery within 24 hours, multifetal pregnancy, prelabour rupture of membranes, known fetal anomalies, underlying maternal medical disease or contraindication to expectant treatment were excluded. Women were monitored for 24 hours and received betamethasone for fetal lung maturity, and magnesium sulphate and antihypertensives were used to stabilise their condition. Those women whose condition became stable started expectant management including bed rest, maternal monitoring, oral antihypertensives, fetal assessment with ultrasonography and, when available, umbilical artery Doppler velocimetry. Daily non-stress testing was done and biophysical profile (BPP) was obtained when needed. The study included 155 women with a mean maternal age of 28.9 ± 6.1 years and a mean gestational age at admission of 30.2 ± 2.4 weeks. The incidence of IUGR (less than 10th percentile) was 58.7% (91 of 155 pregnancies). Mean gestational age at delivery was 30.9 ± 2.1 weeks. When comparing maternal adverse outcomes between mothers whose babies were SGA and those whose babies were appropriately grown, no statistically significant differences were found with respect to renal insufficiency, pulmonary oedema, eclampsia or placental abruption. Similarly, no statistically significant differences were found in terms of neonatal complications between the two groups (intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia, sepsis, respiratory distress syndrome or sepsis). It was also found that the incidence of respiratory distress syndrome and other morbidities (intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia, sepsis and Apgar score less than 7 at 5 minutes) markedly decreased after 30 weeks. When stratified for both gestational age and IUGR up to or greater than 5th percentile, gestational age appeared to be the best predictor of good neonatal outcome, and after 30 weeks the incidence of neonatal complications decreased by two-thirds.

A retrospective population study undertaken in the Trent region of the UK between 1994 and 1997 involved live births, stillbirths and late fetal losses (excluding congenital malformations) from 22 to 32 weeks; 3760 babies who were white European or Asian were included.[142] [EL = 2+] The study was undertaken to establish birthweight and gestational age-specific survival rates and to create easy-to-use tables to guide decision-making with respect to timing of delivery. Not surprisingly, survival rates increased with increasing fetal size and gestational age. However, they also were higher in infants of Asian women compared with those of white European women.

A prospective cohort study from the USA looked at mortality and morbidity rates at a corrected age of 18–22 months in 4446 babies born at 22–25 weeks of gestation.[143] [EL = 2++] At 18–22 months, 49% of the babies had died, 61% had died or had profound impairment, and 73% had died or had impairment. Mortality and morbidity rates by gestational age at birth are summarised in Table 7.2.

Table 7.2 Mortality and morbidity rates at 18–22 months by gestational age at birth

Gestation	Outcome		
	Dead	Dead or profound impairment	Dead or impairment
22 weeks	95%	98%	99%
23 weeks	74%	84%	91%
24 weeks	44%	57%	72%
25 weeks	25%	38%	54%

HELLP syndrome

A retrospective cohort study conducted in the Netherlands compared fetal and maternal outcome of pre-eclampsia, with and without HELLP syndrome, to determine whether expectant management increased the risk of perinatal mortality in women with HELLP syndrome.[144] [EL = 2+] Women in the two groups (102 in total, 51 women in each) were matched according to parity (primigravida or multigravida) and gestational age on admission (up to 12 days' difference). There was no statistically significant difference in the mean diastolic blood pressure between the two groups. Systolic blood pressure, however, was statistically significantly higher in the HELLP group ($P < 0.001$). Women with pre-existing diseases were excluded. All women underwent expectant management including bed rest, sodium-restricted diet (~400 mg/24 hours), antihypertensive treatment (if diastolic blood pressure exceeded 115 mmHg) and anticonvulsant treatment, together with non-invasive monitoring of the fetal and maternal condition. The median interval between admission and delivery was 3 days (range 0–59 days) in the HELLP syndrome group and 9 days (range 0–63 days) in the group without HELLP syndrome. No cases of maternal mortality, pulmonary oedema or renal insufficiency were reported. The incidence of eclampsia and placental abruption was not statistically significantly different between the two groups. Similarly, no statistically significant differences were reported for perinatal death or other neonatal complications (cerebral bleeding, artificial ventilation, sepsis or major handicaps). Multivariate regression analysis using diagnosis of HELLP syndrome or pre-eclampsia, gestational age at admission, parity, the need for antihypertensive treatment, eclampsia, haematocrit and plasma creatinine as independent variables demonstrated statistically significant effects of gestational age (RR 1.4; 95% CI 1.1 to 1.7 per week of gestation) and antihypertensive treatment (RR 3.6; 95% CI 1.02 to 12.4).

Cost effectiveness

The literature search did not identify any published economic evaluations comparing immediate birth with expectant management in women who have pre-eclampsia with mild or moderate hypertension preterm (34–37 weeks). In view of the lack of published cost-effectiveness evidence, the GDG requested an original health economic analysis to help in the formulation of guideline recommendations. The results of this analysis are summarised below, and further details of the analysis are presented in Appendix J.

There are no published clinical effectiveness trials comparing immediate birth with expectant management in women who have pre-eclampsia with mild or moderate hypertension at 34–37 weeks. However, for this health economic model data were used from a retrospective case–control study undertaken in the USA.[145] The study presented a secondary analysis of neonatal outcomes by week of delivery between 35 and 37 weeks. Neonatal outcomes for the immediate birth arm of the model were those reported in the study at 35 weeks. The outcomes for expectant management were assumed to be those reported at weeks 36 and 37. A decision tree was constructed in Excel™ and TreeAge Pro® to estimate the cost effectiveness of the two strategies (immediate birth versus expectant management).

The model demonstrated that immediate birth was cost effective compared with expectant management in women who have pre-eclampsia with mild or moderate hypertension preterm at the NICE £20,000 per QALY willingness to pay threshold, with an estimated ICER of £2,900 per QALY. The robustness of the base-case results was explored using univariate sensitivity analysis. The model results were sensitive to assumptions made in the model about incidence of severe disease. The GDG is aware that this result needs to be interpreted with caution because of the lack of comparative data for the two strategies. The GDG is also aware of a continuing RCT (the Hypertension and Pre-eclampsia Intervention Trial in the Almost Term patient (HYPITAT-II) comparing the two strategies; this open-label multicentre trial is funded by the Netherlands Organisation for Health Research and Development and plans to complete by December 2011 (see www.trialregister.nl/trialreg/admin/rctview.asp?TC=1792).

Evidence statement

Pooled results from two good-quality RCTs [EL = 1++ and EL = 1+] indicate that babies whose mothers underwent early delivery had increased risk of hyaline membrane disease and necrotising enterocolitis. In one, the babies were more likely to need admission to NICU than

those whose mother received expectant management. In the other, babies in the early delivery group were less likely to be SGA. No statistically significant differences were found in terms of the maternal outcomes development of HELLP syndrome, placental abruption, need for caesarean section or eclampsia.

An RCT that investigated the appropriate timing of delivery in pregnancies between 24 and 36 weeks when there was potential fetal compromise showed no overall difference in perinatal outcome between immediate and delayed delivery groups. In 46% of the immediate delivery group and 40% of the delayed delivery group the pregnancy was complicated by hypertension. Two-year follow-up also showed no statistically significant difference in the rate of death or disability between the groups.

Another retrospective study [EL = 2+] of the expectant management of severe pre-eclampsia before 34 weeks showed that neonatal outcome was related to gestational age at birth rather than the degree of growth restriction.

A retrospective study [EL = 2+] showed that expectant management of pre-eclampsia with and without HELLP syndrome resulted in similar maternal and perinatal outcomes.

Health economic modelling suggests that immediate birth is cost effective, although the GDG appreciates the data limitations of the analysis.

GDG interpretation of the evidence

The evidence shows a clear association between immediate preterm birth and increased neonatal morbidity with no apparent decrease in maternal morbidity in women with severe pre-eclampsia, although studies of expectant management excluded women with serious complications. With this caveat in mind, the GDG concluded that expectant management of severe pre-eclampsia, with or without HELLP syndrome, should be considered unless there are clear maternal or fetal indications for immediate birth. The GDG's view is that the lack of evidence of benefit in prolonging pregnancy beyond 34 weeks in women with severe pre-eclampsia justifies offering birth after 34 weeks. The economic analysis also showed that offering birth after 34 weeks is cost effective, and that the incidence of severe disease is the main determinant of cost effectiveness.

Although IUGR was excluded from some of the studies of expectant management and there was evidence that survival of preterm babies may be lower than that of SGA babies, the GDG felt that there were no strong grounds for offering birth before 34 weeks in women with pre-eclampsia simply on the basis of poor fetal growth. Similarly, the presence of HELLP syndrome alone should not influence timing of birth.

No evidence was identified in relation to the consequences for the mother and baby of conservative (expectant) management in women who have pre-eclampsia with mild or moderate hypertension at or before 36 weeks, although one RCT provided clear evidence of the clinical and cost effectiveness of immediate birth after 36 weeks.

The GDG feels that, as a proportion of women who have pre-eclampsia with mild or moderate hypertension will progress to severe pre-eclampsia, which is associated with serious adverse outcomes, an offer of immediate birth should be considered. The GDG appreciates that other factors, both maternal and fetal, and the availability of neonatal intensive care may affect the precise timing. The HYPITAT trial confirmed that there is no maternal or immediate neonatal disadvantage with immediate birth after 37^{+0} weeks in women who have pre-eclampsia with mild or moderate hypertension. The adverse consequences for the woman and the baby of progression to severe pre-eclampsia are greater than those for women with mild or moderate gestational hypertension who progress to severe hypertension (see Section 6.7), and the rate of progression to severe pre-eclampsia is unpredictable. The GDG thus recommends birth within 24–48 hours for women who have pre-eclampsia with mild or moderate hypertension after 37^{+0} weeks.

Biochemical and haematological parameters (including the degree of proteinuria) are poor predictors of maternal and fetal outcomes, making it difficult to give specific values to guide decision-making about timing of birth. In general, the GDG felt that there were no grounds for recommending birth based on any absolute threshold: the disease process differs between women and there is interaction in clinical terms between maternal multisystem involvement,

blood pressure and fetal status. The GDG's view is that a consultant or specialist review of the individual case is essential and that a care plan should be developed to include the acceptable thresholds of all monitored variables for each pregnancy.

Recommendations

Manage pregnancy in women with pre-eclampsia conservatively (that is, do not plan same-day delivery of the baby) until 34 weeks.

Consultant obstetric staff should document in the woman's notes the maternal (biochemical, haematological and clinical) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia.

Consultant obstetric staff should write a plan for antenatal fetal monitoring during birth.

Offer birth to women with pre-eclampsia before 34 weeks, after discussion with neonatal and anaesthetic teams and a course of corticosteroids has been given if:

- severe hypertension develops refractory to treatment
- maternal or fetal indications develop as specified in the consultant plan.

Recommend birth for women who have pre-eclampsia with severe hypertension after 34 weeks when their blood pressure has been controlled and a course of corticosteroids has been completed (if appropriate).

Offer birth to women who have pre-eclampsia with mild or moderate hypertension at 34^{+0} to 36^{+6} weeks depending on maternal and fetal condition, risk factors and availability of neonatal intensive care.

Recommend birth within 24–48 hours for women who have pre-eclampsia with mild or moderate hypertension after 37^{+0} weeks.

Research recommendation

When should women who have pre-eclampsia with mild or moderate hypertension give birth?

Why this is important

There is a 'grey' zone for women who have pre-eclampsia with mild or moderate hypertension between 34 and 37 weeks when the optimal timing of birth is not clear.

Women who have pre-eclampsia with mild or moderate hypertension may progress to severe disease with its risks, but it is not clear whether these risks outweigh or should outweigh the risks of planned late preterm birth for the baby. Neonatal services are under constant pressure and planned preterm birth without clear benefit to either woman or baby would have costs.

Randomised controlled trials should be carried out that compare policies of immediate planned birth between 34^{+0} and 36^{+6} weeks in women who have pre-eclampsia with mild or moderate hypertension with expectant management and birth for clinical progression. Outcomes should include severe pre-eclampsia and its complications, need for critical care, maternal satisfaction, neonatal morbidity and mortality, and health economics. Trials need to be large enough to examine less common complications in the woman.

7.8 Postnatal investigation, monitoring and treatment (including after discharge from critical care)

Clinical effectiveness

A single literature search was conducted for the various investigations and interventions covered. The population comprised postnatal women who presented with pre-existing hypertensive disorders or with new hypertension during their pregnancies. The search identified 1979 references, of which 31 were retrieved. There was no evidence for observations or monitoring.

Antihypertensives

Six RCTs were identified, two of which[146;147] were EL = 1+, and four of which[127;148-150] were EL = 1–.

Need for antihypertensive agents postnatally

A small RCT from the USA investigated the efficacy of nifedipine in controlling hypertension and improving urine output in postpartum women with severe pre-eclampsia.[148] [EL = 1–] Women were randomly allocated (using a random number table) to either receive nifedipine 10 mg orally every 4 hours for 48 hours immediately after delivery ($n = 16$) or placebo ($n = 15$). The process of concealment allocation was adequate. Baseline characteristics of women from each group were comparable.

There were no women in either group who needed additional antihypertensive therapy. There was also no change in treatment due to maternal side effects in either group or any reported cases of significant hypotension.

Hydralazine versus labetalol

An RCT conducted in Panama compared two antihypertensive agents postnatally in women with severe hypertensive disorders.[146] [EL = 1+] Eighty-two women were randomly allocated using a computer-generated list by means of sequentially numbered opaque sealed envelopes to either receive intravenous hydralazine 5 mg bolus repeated every 20 minutes ($n = 42$) or intravenous labetalol 20 mg bolus followed by 40 mg increased up to 300 mg ($n = 40$). Baseline characteristics for women from each group were comparable.

No statistically significant differences were found in terms of 'symptoms', palpitations, headache or tachycardia between the groups. Women receiving 1–2 doses or 3–4 doses for effective blood pressure control did not differ statistically significantly between the two groups. There was also no statistically significant difference in those who developed HELLP syndrome or oliguria.

Timolol versus methyldopa

An RCT from the UK compared the use of timolol and methyldopa in the management of puerperal hypertension.[127] [EL = 1–] Untreated postpartum women with diastolic blood pressure of 95–105 mmHg were randomly allocated to either receive timolol 5 mg orally three times a day ($n = 40$) or methyldopa 250 mg orally three times a day ($n = 40$). In both cases, the dose was doubled every 24 hours twice if diastolic blood pressure was above 95 mmHg. Antenatally, 46 of the 80 women had received drug treatment for hypertension and another 14 had had mild hypertension (diastolic blood pressure below 95 mmHg) that did not require treatment. The remaining 20 women were not hypertensive before delivery.

There was no statistically significant difference in the need for additional antihypertensive therapy between the two groups (three of 40 versus one of 40: RR 3.00; 95% CI 0.33 to 27.63). There was also no statistically significant difference in the number of those who had their medications changed owing to maternal side effects (one of 40 versus two of 40: RR 0.50; 95% CI 0.05 to 5.30).

Hydralazine versus methyldopa

An RCT from the USA compared the effects of hydralazine and methyldopa on mean arterial blood pressure and urinary output in the first 24 hours postpartum in women with severe postpartum or intrapartum hypertension and proteinuria.[150] [EL = 1–] Women with a history of chronic hypertension or hepatic disease and those who had antihypertensive treatment during pregnancy other than that used intrapartum were excluded. Twenty-six women were randomly allocated by selecting a sealed opaque envelope containing randomly generated numbers to receive either intramuscular hydralazine 20 mg every 6 hours ($n = 12$) or intravenous methyldopa 250 mg every 6 hours ($n = 14$).

There were no statistically significant differences in the need to augment the dose between the two groups. There were no women in either of the two groups who needed additional antihypertensive therapy or change in treatment owing to maternal side effects.

Diuretics

An RCT from the USA investigated whether a brief postpartum course of furosemide for women with pre-eclampsia benefited recovery and shortened hospitalisation.[147] [EL = 1+] Two hundred sixty-four women with hypertension during their pregnancies were enrolled in the study (169 women had mild pre-eclampsia, 70 had severe pre-eclampsia or HELLP syndrome and 25 had chronic hypertension with superimposed pre-eclampsia). The women were randomly assigned by opening the next previously prepared sequential and numbered opaque study envelope to either receive furosemide 20 mg daily together with an oral potassium supplement 20 mEq daily for 5 days or to receive no medication (no placebo was used in the non-interventional arm). Baseline characteristics were comparable between the two groups.

Women treated with furosemide were statistically significantly less likely to need additional antihypertensive medication during hospitalisation in comparison with those who received no medication (46 of 132 versus 62 of 132: RR 0.74; 95% CI 0.55 to 0.997). With regard to the use of additional antihypertensive medication at time of hospital discharge, there was no statistically significant difference between the two groups (38 of 132 versus 49 of 132: RR 0.78; 95% CI 0.55 to 1.10). However, when results were stratified by type of hypertensive disorder, the only outcome that became statistically significant was the need for additional antihypertensive in women with severe pre-eclampsia/HELLP syndrome (two of 35 versus nine of 35: RR 0.22; 95% CI 0.05 to 0.96).

A small RCT from the UK investigated diuretics used postnatally to lower blood pressure in women with severe pre-eclampsia and consequently shorten their hospital stay and need for professional supervision.[149] [EL = 1−] Nineteen women with severe pre-eclampsia were randomly allocated to receive either furosemide 40 mg/day orally ($n = 10$) or placebo ($n = 8$) in a double-blind trial.

There was no statistically significant difference in the need for antihypertensive medication between the two groups (three of ten versus three of eight: RR 0.8; 95% CI 0.22 to 2.93). Oliguria at discharge did not differ statistically significantly between the two groups (three of ten versus two of eight: RR 1.2; 95% CI 0.26 to 5.54).

Evidence statement

Three trials have compared the effectiveness of various antihypertensive drugs (hydralazine versus labetalol, timolol versus methyldopa, hydralazine versus methyldopa). Results from these trials (one with EL = 1+ and the other two with EL = 1−) suggest no beneficial effect of one drug over the other.

Antihypertensive drugs and breastfeeding

The evidence for this is discussed in Chapter 11.

Use of magnesium sulphate in the postnatal period

No evidence was identified to inform the GDG about the use of magnesium sulphate in the postnatal period.

Investigation and management of women with pre-eclampsia in the postnatal period

No evidence was identified to inform the GDG about preferred investigations and treatment.

GDG interpretation of the evidence

There was lack of good-quality RCTs to determine whether routine antihypertensive treatment should be given to women with pre-eclampsia after birth or which drug should be used, as the included trials evaluated different antihypertensive drugs.

A good-quality trial found women treated with furosemide were less likely to need additional antihypertensive medications during hospitalisation than those treated with placebo but the difference was only just statistically significant; no such difference was found at the time of hospital discharge, except in the subgroup of women with severe pre-eclampsia/HELLP syndrome. Two other small trials found no evidence of benefit for using either diuretics or nifedipine in the postnatal period.

Although there was no specific evidence dealing with the postnatal period, the GDG view was that the principles established for investigation and observation relevant to the antenatal period also applied to this period.

The GDG considers that an individualised care plan should be established before transfer to community care. The GDG's view is that women with pre-eclampsia should be offered a formal medical review at the postnatal review (6–8 weeks after the birth). Who provides this review will depend on local circumstances and the level expertise of individual healthcare professionals, and so the GDG was not able to be prescriptive on this point. However, the woman's care plan should document who will provide follow-up care, including medical review if required. The medical review should include measurement of blood pressure, urine testing and review of antihypertensive drugs.

Symptoms of impending eclampsia can occur in women after birth and should be enquired about at each assessment. Blood pressure measurements should be undertaken with the same regularity as in the antenatal period and practitioners should be aware that blood pressure has a tendency to rise 4 or 5 days after birth.

The same blood indices should be monitored until they are clearly progressing into the normal range for a non-pregnant woman. Abnormal results at 6 weeks may indicate an abnormality that requires further investigation.

Both persistent significant proteinuria (2+ on dipstick) and blood pressure that still requires control by antihypertensives 6 weeks after birth should be regarded as abnormal and require a specialist assessment. Chronic hypertension in women who had pre-eclampsia should be diagnosed and managed in accordance with 'Hypertension', NICE clinical guideline 34.[3]

Recommendations

In women with pre-eclampsia who did not take antihypertensive treatment and have given birth, measure blood pressure:

- at least four times a day while the woman is an inpatient
- at least once between day 3 and day 5 after birth
- on alternate days until normal if blood pressure was abnormal on days 3–5.

In women with pre-eclampsia who did not take antihypertensive treatment and have given birth, start antihypertensive treatment if blood pressure is 150/100 mmHg or higher.

Ask women with pre-eclampsia who have given birth about severe headache and epigastric pain each time blood pressure is measured.

In women with pre-eclampsia who took antihypertensive treatment and have given birth, measure blood pressure:

- at least four times a day while the woman is an inpatient
- every 1–2 days for up to 2 weeks after transfer to community care until the woman is off treatment and has no hypertension.

For women with pre-eclampsia who have taken antihypertensive treatment and have given birth:

- continue antenatal antihypertensive treatment
- consider reducing antihypertensive treatment if their blood pressure falls below 140/90 mmHg
- reduce antihypertensive treatment if their blood pressure falls below 130/80 mmHg.

If a woman has taken methyldopa† to treat pre-eclampsia, stop within 2 days of birth.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

Offer women with pre-eclampsia who have given birth transfer to community care if all of the following criteria have been met:

- there are no symptoms of pre-eclampsia
- blood pressure, with or without treatment, is 149/99 mmHg or lower
- blood test results are stable or improving.

Write a care plan for women with pre-eclampsia who have given birth and are being transferred to community care that includes all of the following:

- who will provide follow-up care, including medical review if needed
- frequency of blood pressure monitoring
- thresholds for reducing or stopping treatment
- indications for referral to primary care for blood pressure review
- self-monitoring for symptoms.

Offer women who have pre-eclampsia and are still on antihypertensive treatment 2 weeks after transfer to community care a medical review.

Offer all women who have had pre-eclampsia a medical review at the postnatal review (6–8 weeks after the birth).

Offer women who have had pre-eclampsia and who still need antihypertensive treatment at the postnatal review (6–8 weeks after the birth) a specialist assessment of their hypertension.

In women who have pre-eclampsia with mild or moderate hypertension or after step-down from critical care:

- measure platelet count, transaminases and serum creatinine 48–72 hours after birth or step-down
- do not repeat platelet count, transaminases or serum creatinine measurements if results are normal at 48–72 hours.

If biochemical and haematological indices are improving but stay within the abnormal range in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated and at the postnatal review (6–8 weeks after the birth).

If biochemical and haematological indices are not improving relative to pregnancy ranges in women with pre-eclampsia who have given birth, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated.

In women with pre-eclampsia who have given birth, carry out a urinary reagent-strip test at the postnatal review (6–8 weeks after the birth).

In women with pre-eclampsia who have given birth and have stepped down from critical care level 2, do not measure fluid balance if creatinine is within the normal range.

Offer women who had pre-eclampsia and still have proteinuria (1+ or more) at the postnatal review (6–8 weeks after the birth) a further review at 3 months after the birth to assess kidney function and consider offering them a referral for specialist kidney assessment.

8 Fetal monitoring

8.1 Introduction

The fetus of a woman with hypertension in pregnancy may be at risk of increased perinatal mortality and morbidity. A single literature search was conducted for the various monitoring methods covered. The population studied was women who presented with pre-existing hypertensive disorders, gestational hypertension or pre-eclampsia during their pregnancies. The search identified 794 references, of which ten are included. There were no specific studies dealing with fetal surveillance in pregnancies complicated by chronic hypertension, gestational hypertension or pre-eclampsia but the results below are likely to be applicable to all three types of hypertensive disorder. This is because the central problem for all pregnancies complicated by any form of hypertension is placental insufficiency with a final common path of effect, which is IUGR, fetal hypoxia and ultimately fetal death.

8.2 Fetal biometry

Clinical effectiveness

There were no RCTs or systematic reviews to provide evidence for the use of fetal biometry in pregnancies complicated by hypertensive disorders.

GDG interpretation of the evidence

There was a lack of relevant evidence for the use of biometry in hypertensive disorders. However, because of the recognised risk of IUGR in this group, the GDG felt that there was a need for the rational use of biometry within its recommendations.

8.3 Umbilical artery Doppler velocimetry

Clinical effectiveness

Women with hypertensive disorders of pregnancy

Two RCTs[151;152] [EL = 1+] were identified that reported data on the use of umbilical artery Doppler velocimetry for fetal assessment in women with hypertensive disorders in pregnancy.

One RCT from South Africa assessed whether the results of umbilical artery Doppler velocimetry were beneficial to the management of a high-risk pregnancy.[152] [EL = 1+] The women recruited were divided into three groups based on the outcomes of Doppler velocimetry examinations: Group 1 ($n = 20$) comprised those with fetuses with absent end-diastolic velocities, Group 2 ($n = 89$) comprised those with hypertension but with fetuses with end-diastolic velocities and Group 3 ($n = 104$) comprised those with fetuses suspected of being SGA but with end-diastolic velocities.

For the hypertensive subgroup (Group 2), women were randomised either into the study group in which Doppler velocimetry was revealed to clinicians ($n = 47$) or into the control group in which Doppler velocimetry was withheld from clinicians ($n = 42$). Randomisation was achieved using a balanced block technique and allocation was inserted into an opaque sealed envelope.

There were no statistically significant differences between the two groups in terms of perinatal death (9% versus 2%: RR 3.57; 95% CI 0.42 to 30.73), antenatal fetal distress (4% versus 2%: RR 1.79; 95% CI 0.17 to 19.01) or NICU admissions (26% versus 26%: RR 0.97; 95% CI 0.48 to 1.9). There were also no statistically significant differences in gestation at delivery, birthweight, hospitalisation for either the woman or the infant, spontaneous labour or caesarean section.

One RCT from Canada compared the use of umbilical artery Doppler velocimetry with non-stress test in women with a high-risk pregnancy ($n = 1340$).[151] [EL = 1+] Participants were at 32 weeks or later and had hypertensive disorders, diabetes that required insulin, suspected IUGR, were postdates or had a patient-perceived decrease in fetal land known fetal cardiovascular anomaly, and women in a subsequent pregnancy if they had participated in the study in a previous pregnancy. Participants were randomly allocated by opening sequentially numbered opaque envelopes generated by a random number table. Women were either allocated to the Doppler velocimetry group ($n = 649$) or to the electronic fetal heart rate using the non-stress test group ($n = 691$). Doppler velocimetry used elevated systolic/diastolic waveform ratios and absent or reversed end-diastolic blood flow as an indication for delivery or induction within 24 hours. Baseline characteristics were not different between the two groups.

The study reported subgroup analysis for incidence of caesarean section for fetal distress. Women who had hypertensive disorders were statistically significantly less likely to have a caesarean section for fetal distress if they were in the Doppler velocimetry group than if they were in the non-stress test group (one of 67 versus 11 of 81: RR 0.11; 95% CI 0.02 to 0.83).

Women with high-risk pregnancies

A systematic review[153] [EL = 1++] and an additional later RCT[151] [EL = 1+] were identified.

The systematic review included 13 RCTs published between 1987 and 1994 (the overall number of participants was 8633) that looked at the use of umbilical artery Doppler velocimetry in high-risk pregnancies (published and unpublished reports) in comparison with no Doppler velocimetry or with routine monitoring.[153] [EL = 1++] The RCTs were divided into 'well-defined' studies (six of 13 studies, $n = 2159$). These comprised only singleton pregnancies with suspected IUGR ($n = 1307$) and/or hypertensive disease of pregnancy ($n = 852$). The 'general-risk' studies (seven of 13 studies, $n = 6474$) had wider and/or poorly defined inclusion criteria: 12–51% suspected IUGR, 12–46% hypertensive disease, 5–38% reduced fetal movements, 4–35% post-term, 4–12% antepartum haemorrhage and 6–44% other high-risk complications.

Twelve of the included studies used adequate randomisation and concealment methods while one used a quasi-randomised approach.

For interpretation of waveform indices, three studies among the well-defined studies used pulsatility index, two used resistance index and one used systolic/diastolic ratio. Four of the general-risk studies used resistance index and one used pulsatility index, and three RCTs used systolic/diastolic ratio.

Perinatal mortality of non-malformed singletons was statistically significantly less in babies born to high-risk women monitored with umbilical artery Doppler velocimetry (OR 0.67; 95% CI 0.47 to 0.97), who were also less likely to have low Apgar score at 5 minutes (OR 0.89; 95% CI 0.74 to 0.97). Women monitored with Doppler velocimetry were less likely to be admitted antenatally (OR 0.56; 95% CI 0.43 to 0.72) and to require emergency caesarean section (OR 0.85; 95% CI 0.74 to 0.97).

When considering all high-risk studies, there was no statistically significant difference between the two groups in terms of induction of labour, elective delivery, admission to NICU or caesarean section. However, subgroup analysis of well-defined studies showed women monitored with umbilical artery Doppler velocimetry to be statistically significantly less likely to be induced (OR 0.78; 95% CI 0.63 to 0.96) or to have elective delivery (OR 0.73; 95% CI 0.61 to 0.88) or caesarean section (OR 0.78; 95% CI 0.65 to 0.94).

One RCT from Canada (described above) investigated the use of umbilical artery Doppler velocimetry for screening high-risk pregnancies.[151] [EL = 1+] It showed women with high-risk pregnancy to be more likely to be induced as a result of abnormal testing (31 of 649 versus 13 of 691: RR 2.53; 95% CI 1.34 to 4.81) but less likely to have caesarean section delivery for fetal distress (30 of 649 versus 60 of 691: RR 0.53; 95% CI 0.35 to 0.81). However, there were no statistically significant differences in terms of Apgar score less than 4 at 1 minute, Apgar score less than or equal to 7 at 5 minutes, vaginal operative delivery, caesarean section delivery excluding fetal distress as an indication, admission to NICU or birthweight. There was only one stillbirth case and it was in the no Doppler velocimetry group.

Evidence statement

Women with hypertensive disorders of pregnancy

Evidence from two relatively small RCTs [EL = 1+] showed no statistically significant improvement in neonatal outcomes including death and admission to NICU in infants of women with hypertensive disorders monitored by umbilical artery Doppler velocimetry. However, women were less likely to require a caesarean section for fetal distress if Doppler velocimetry was used.

Women with high-risk pregnancies

One systematic review [EL = 1++] showed that use of umbilical artery Doppler velocimetry for fetal assessment in women with high-risk pregnancies reduced perinatal mortality and babies born with low Apgar score at 5 minutes. Women monitored with umbilical artery Doppler velocimetry were less likely to be admitted antenatally and to require emergency caesarean section. Subgroup analysis of well-defined studies showed women monitored with umbilical artery Doppler velocimetry to be statistically significantly less likely to be induced or to have elective delivery or caesarean section.

One additional RCT [EL = 1+] showed women with high-risk pregnancy monitored with umbilical artery Doppler velocimetry to be more likely to be induced as a result of abnormal testing but less likely to have caesarean section delivery for fetal distress.

GDG interpretation of the evidence

While one study that dealt with hypertensive pregnancies appeared to show no benefit of umbilical artery Doppler velocimetry, other studies in generally high-risk pregnancies, of which hypertension was a component, demonstrated advantages in terms of reduced perinatal mortality and better decision-making. Although no formal health economic modelling was undertaken, the systematic review shows reductions in perinatal mortality and serious maternal and perinatal morbidity such that the GDG considered that it would almost certainly be cost effective. The GDG feels that these findings can be extrapolated to hypertensive pregnancies generally. There is a lack of evidence about the timing of the test and the frequency with which it should be repeated.

8.4 Cardiotocography

Clinical effectiveness

One Cochrane systematic review looked at RCTs that investigated the use of cardiotocography against alternative methods of assessing fetal health (cardiotocography and withholding the result from the caregiver or a non-monitored group).[154] [EL = 1+] Participants were women at low and high obstetric risk, including women with hypertensive disorders, which composed different percentages of the main sample of all included trials.

In three trials, cardiotocography was performed on all women, who were randomly allocated to revealed (study) or concealed (control) groups. In one trial, women in the control group were not monitored. The trials were conducted from the late 1970s to 1981 at a time when biochemical monitoring with human placental lactogen and estriol were commonly used. Limited ultrasound was also available. Three of the four trials stated that these other methods of monitoring were available to clinicians for both arms of the study.

The quality of the studies varied widely. In two there was true randomisation, and in the other two quasi-randomisation with either birth date or hospital number was used. No study was double blinded and in two trials it was not possible to estimate the number of exclusions.

There was a trend towards more perinatal mortality in the cardiotocography group (three RCTs, $n = 1279$; Peto OR 2.65; 95% CI 0.99 to 7.12). Furthermore, more women were admitted to hospitals (one RCT, $n = 300$; Peto OR 0.37; 95% CI 0.17 to 0.83) and more women remained in hospital (one RCT, $n = 300$; Peto OR 0.43; 95% CI 0.21 to 0.89) in the cardiotocography group. No statistically significant differences were found in onset of labour (spontaneous, elective ceasarean section or labour induction) or method of delivery (normal vaginal birth, operative

vaginal birth or caesarean section). There were also no statistically significant differences in fetal distress, abnormal neurological signs, abnormal Apgar score or neonatal admission.

Evidence statement

A Cochrane systematic review [EL = 1+] showed that women with low- or high-risk pregnancies monitored with cardiotocography had no significantly different outcomes from those who were not monitored. Indeed, there tended to be higher perinatal mortality risk in babies of women monitored with cardiotocography.

GDG interpretation of the evidence

The evidence in favour of antenatal cardiotocography is not encouraging and yet it is probably one of the most commonly performed tests in pregnancy. The GDG recognises that any attempt to withdraw its use completely would be unacceptable but recommends that its use should be rationalised such that there are clear indications for repeat testing, such as where the woman reports a change in fetal movement or has vaginal bleeding or abdominal pain.

8.5 Routine versus computerised cardiotocography in severe pre-eclampsia

Clinical effectiveness

One RCT from South Africa compared the use of computerised cardiotocography with routine cardiotocography in monitoring fetal heart rate of women with severe early-onset pre-eclampsia (gestational age 28–34 weeks) whose pregnancies were managed expectantly.[136] [EL = 1+] The study included 59 women who were allocated by random numbers generated by computer and enclosed in successively numbered sealed opaque envelopes into either the computerised cardiotocography group ($n = 29$) or the routine cardiotocography group ($n = 30$) groups. Women at 28–31 weeks were randomised separately from the group at 32–34 weeks to ensure equal distribution of gestational age in the two groups. During labour, all fetal heart-rate monitoring was done with a computerised monitor and visually assessed.

The study showed no statistically significant differences in perinatal loss (four of 29 versus one of 30: RR 4.13; 95% CI 0.49 to 34.86), perinatal morbidity (13 of 29 versus 14 of 30: RR 0.96; 95% CI 0.55 to 1.68) or admission to NICU (nine of 29 versus nine of 30: RR 1.03; 95% CI 0.48 to 2.23) between the two groups. There were also no statistically significant differences in caesarean sections or Apgar score less than 7 at 5 minutes. Standard deviation for gestation, weight, days gained before delivery, duration of stay at NICU and duration of recordings were not reported.

Evidence statement

One small RCT [EL = 1–] showed no difference between the uses of computerised and routine cardiotocography in women with severe pre-eclampsia in terms of perinatal loss, perinatal morbidity or admission to NICU.

GDG interpretation of the evidence

The GDG sees no obvious benefit to the use of computerised cardiotocography in hypertensive pregnancies

8.6 Biophysical profile

Clinical effectiveness

One Cochrane systematic review assessed the effect of the biophysical profile (BPP) when compared with conventional monitoring (cardiotocography only or modified BPP).[155] [EL = 1+] Participants were at 24 weeks or later with singleton high-risk pregnancies. The review included five trials. In one RCT ($n = 145$) women had post-term pregnancy, and in another RCT ($n = 135$)

women had rupture of membrane. In the other three RCTs included, women had a variety of high-risk pregnancies, of which hypertension composed 12%, 12% and 27% of the sample studied. Modified BPP comprised cardiotocography and ultrasound measurement of the amniotic fluid. Both randomised and quasi-randomised controlled trials were included (two RCTs were adequately randomised, two were quasi-randomised and randomisation was not clear in one). Blinding was either not reported or not conducted in two RCTs.

Four studies ($n = 2829$) compared BPP with cardiotocography. One trial ($n = 145$) compared complete BPP with cardiotocography and amniotic fluid assessment using the single deepest vertical pocket technique. Pregnancies were managed on the basis of normal or abnormal test results. Although not all trials reported the gestational age range of included pregnancies, it is of interest to note that the majority of included pregnancies were at or close to term (36.2 to greater than 42 weeks in four RCTs, $n = 2829$), whereas the mean gestational age in one RCT ($n = 135$) was 24.2 weeks.

Babies born to women monitored with BPP stayed for shorter periods in NICU (two RCTs, $n = 1442$; standard mean difference (MD) 0.20 days; 95% CI 0.09 to 0.30 days). However, data on length of stay were skewed owing to gross prematurity in one RCT ($n = 135$) and are therefore unreliable. Women in the BPP group were more likely to be induced in general (one RCT, $n = 145$; RR 1.45; 95% CI 1.04 to 2.03) and induced for abnormal fetal assessment (one RCT, $n = 135$; RR 2.58; 95% CI 1.39 to 4.78).

There were no statistically significant differences in perinatal deaths or admission to NICU between the two groups. Similarly, no statistically significant differences were found in Apgar score less than 7 at or after 5 minutes, SGA, meconium, respiratory distress syndrome or caesarean section for fetal distress. However, subgroup analysis of the high-quality trials showed a statistically significantly higher level of caesarean section in the BPP group (two RCTs, $n = 280$; RR 1.60; 95% CI 1.05 to 2.4).

Evidence statement

A Cochrane systematic review[155] [EL = 1+] that investigated the use of BPP in women with high-risk pregnancy found no statistically significant differences between those monitored by BPP and those monitored by cardiotocography or modified BPP in terms of perinatal death or admission to NICU. It also showed no statistically significant differences in Apgar score less than 7 at or after 5 minutes, SGA or caesarean section. Women monitored with BPP were statistically significantly more likely to be induced.

GDG interpretation of the evidence

The evidence does not support the use of BPP in pregnancies complicated by hypertension.

8.7 Amniotic fluid index versus single deepest vertical pocket

Clinical effectiveness

A Cochrane systematic review compared the use of amniotic fluid index with the use of the single deepest vertical pocket measurement as a screening tool for decreased amniotic volume in preventing adverse pregnancy outcome.[156] [EL = 1++] The review looked at RCTs involving women with a singleton pregnancy, whether at low or high risk, undergoing tests for assessment of fetal wellbeing.

Four RCTs ($n = 3125$) were included. All four trials were of high quality and all included trial reports that noted adequate concealment of allocation. All had less than 5% of participant loss. In one trial, the caregivers were blinded to the group assignment and the specific measurement; in the others, blinding of participants, caregivers and outcome assessment was unclear.

One of the included trials ($n = 500$) studied post-term pregnant women. In the three other trials, the sample studied was women with high-risk pregnancies with a proportion of those with hypertension (102 of 537, 88 of 1000 and 127 of 1088). There were 529 (16.9%) participants at

a gestation of less than 37 weeks, 1431 (45.8%) at 37 to 40 weeks, 665 (21.3%) at more than 40 to 42 weeks, and 500 (16.0%) at more than 42 weeks.

No difference was found between the two methods in primary outcomes (admission to NICU and perinatal death).

When the amniotic fluid index was used, statistically significantly more cases of oligohydramnios were diagnosed (four RCTs, $n = 3125$; RR 2.33; 95% CI 1.67 to 3.24) and more women had induction of labour (three RCTs, $n = 2037$; RR 2.10; 95% CI 1.60 to 2.76) and caesarean section for fetal distress (four RCTs, $n = 3125$; RR 1.45; 95% CI 1.07 to 1.97).

No statistically significant differences were found in other secondary outcomes such as umbilical artery pH less than 7.1, Apgar score less than 7 at 5 minutes, presence of meconium, non-reassuring fetal heart-rate tracing, assisted vaginal delivery, assisted vaginal delivery for fetal distress and caesarean section.

Evidence statement

A Cochrane review [EL = 1++] showed that in women with low- or high-risk pregnancies there is no evidence that one method is superior to the other in the prevention of poor perinatal outcomes including admission to NICU, perinatal death, umbilical artery pH less than 7.1, the presence of meconium, Apgar score less than 7 at 5 minutes or caesarean section. When the amniotic fluid index was used, statistically significantly more cases of oligohydramnios were diagnosed and more women had induction of labour and caesarean section for fetal distress.

GDG interpretation of the evidence

The evidence did not relate specifically to pregnancies complicated by hypertension but the comparison between methods of amniotic fluid assessment favoured the single deepest vertical pocket – the amniotic index resulted in more intervention without any clinical benefit for the fetus. The opportunity cost for measurement of amniotic fluid is negligible.

8.8 Fetal movements

Clinical effectiveness

No clinical studies specific to women with hypertensive disorders of pregnancy were identified.

One multicentre cluster RCT, involving women receiving maternity care from an obstetrician, a clinic (no further details reported) or a hospital investigated whether routine formal fetal movement counting, backed by appropriate action, resulted in a clinically important improvement in neonatal outcomes.[157] [EL = 1+] The study recruited 68 654 women (gestational age 28–32 weeks) and divided them into 66 clusters (about 1000 women each). The study included some women with pre-eclampsia but the number was not reported.

Clusters were matched into pairs based on the estimation of risk of antepartum late fetal death and were randomly allocated to the experimental or control policy within the matched pairs (fetal movement count: 33 clusters, $n = 31\,993$; no instruction: 33 clusters, $n = 36\,661$). The randomised groups were similar in terms of maternal age, primiparity and multiple pregnancies. In the experimental group, women were instructed to count fetal movements routinely every day (count-to-ten chart) and to contact the hospital if movements were reduced. In the control group, no instruction was given to women about routinely counting fetal movement but they could still raise concerns and could be asked about fetal movements at antenatal visits, and obstetricians could give charts to selected women when indicated. For both policies, clinicians were asked to respond to reports of reduced movements as they deemed appropriate.

No statistically significant difference was found between the two groups in terms of preventing stillbirth (2.90 ± 0.33 versus 2.67 ± 0.27 stillbirths per 1000 normally formed singleton births; MD 0.24; 95% CI −0.50 to 0.98). Women in the routine counting group were not different from those in the control group in terms of antenatal admission, undergoing cardiotocography, being induced, having elective caesarean section or feeling anxious in late pregnancy.

Evidence statement

A multicentre cluster RCT [EL = 1+] involving women receiving maternity care from an obstetrician, a clinic (no further details reported), or a hospital during treatment, including some women with pre-eclampsia, showed no difference in pregnancy outcomes between women counting fetal movements routinely and those who were not in terms of preventing stillbirths, antenatal admissions, undergoing labour induction or elective caesarean section, or feeling anxious in late pregnancy.

GDG interpretation of the evidence

Evidence shows that formal fetal movement counting confers no benefit in terms of reduced perinatal mortality or intervention in the women receiving maternity care from an obstetrician, a clinic, or a hospital during treatment, including some women with pre-eclampsia. This evidence was also noted in 'Antenatal care', NICE clinical guideline 62.[1] However women with hypertensive disorders of pregnancy should be encouraged to be aware of their baby's movements and to report perceived changes to their healthcare professionals.

8.9 Uterine artery Doppler velocimetry in high-risk pregnancies

Clinical effectiveness

Seven diagnostic studies[74-78;158;159] [EL = II] investigated the use of uterine artery Doppler velocimetry to predict pre-eclampsia in high-risk women. Alterations in blood flow velocity in the uterine arteries were interpreted using the following tests: resistance index of the main artery (peak-systolic flow minus end-diastolic flow divided by peak-systolic flow), notch (early diastolic notch in uterine artery) and albumin : creatinine ratio.

Results are presented below by population stratified according to risk factors: previous pre-eclampsia, chronic hypertension (see Section 3.2), kidney disease and mixed risks. An HTA report[39] and a systematic review and meta-analysis published by the same research team[160] were excluded from the guideline review because they were based on women at low risk, whereas the guideline focus was on women at high risk, and also those already taking aspirin.

Women with previous pre-eclampsia

A prospective diagnostic study studied women with previous pre-eclampsia ($n = 56$; see Table 8.1).[158] [EL = II] Two of these women had had eclampsia and 24 had had early-onset pre-eclampsia (before 34 weeks), 17 had also had IUGR and six had also had intrauterine fetal demise. All women underwent uterine artery Doppler velocimetry at 24 weeks. Low-dose aspirin was given to women from 12 weeks of gestation.

Using an endpoint of pre-eclampsia and the resistance index (abnormal: > 0.58) to interpret the Doppler velocimetry results showed a sensitivity of 100% and a specificity of 60%. Unilateral or bilateral notches showed a sensitivity of 100% and a specificity of 66%, while using both bilateral notches showed a sensitivity of 33% and a specificity of 87%.

Using an endpoint of IUGR and the resistance index (abnormal: > 0.58) to interpret the Doppler velocimetry results showed a sensitivity of 85% and a specificity of 70%. Unilateral or bilateral notches showed a sensitivity of 85% and a specificity of 77%, while using both bilateral notches showed a sensitivity of 46% and a specificity of 95%.

Women with kidney disease

A prospective diagnostic study used uterine artery Doppler velocimetry (19–24 weeks of gestation) in pregnant women with known kidney disease (other than diabetic nephropathy; see Table 8.1).[159] [EL = II] Renal function was considered decreased if two out of the following three were abnormal: plasma creatinine (90 micromol/litre or higher), plasma urea (6.5 mmol/litre or higher), creatinine clearance (1.5 ml/second or lower).

Fifty-one women were included, 24 of whom had primary glomerulonephritis, 19 had reflux nephropathy, five had glomerulonephritis secondary to a systemic disease and three had polycystic kidneys. Of the 51 women, 17 received low-dose aspirin, 17 were treated with the

combination of either aspirin or dipyridamole with subcutaneous low-dose heparin and 17 were untreated during the whole pregnancy.

Using an endpoint of pre-eclampsia and the resistance index (abnormal: > 90th percentile of reference group) to interpret the Doppler velocimetry results showed a sensitivity of 50% and a specificity of 75%. The albumin:creatinine ratio showed a sensitivity of 50% and specificity of 79%.

Using an endpoint of IUGR and the resistance index (abnormal: > 90th percentile of reference group) to interpret the Doppler velocimetry results showed a sensitivity of 83% and a specificity of 80%. The albumin:creatinine showed a sensitivity of 83% and a specificity of 84%.

Women with mixed high-risk factors

Three diagnostic studies[76-78] [EL = II] investigated the use of uterine artery Doppler velocimetry at 22–24 weeks of gestation in women with high-risk pregnancies (previous pre-eclampsia, previous stillbirth, previous placental abruption, previous IUGR, chronic hypertension, diabetes, autoimmune disease, kidney disease, recurrent miscarriage). Descriptions of the included studies are in Table 8.2.

Using the resistance index gave a sensitivity of 78–97% and a specificity of 42–71% on prediction of pre-eclampsia. One of these studies[78] ($n = 116$) reported data on the use of the resistance index in predicting IUGR, which gave a sensitivity of 84% and a specificity of 39%.

Evidence statement

Prediction of pre-eclampsia

Women with previous pre-eclampsia

One diagnostic study [EL = II] showed that uterine artery Doppler velocimetry at 24 weeks of gestation has a sensitivity of 100% and a specificity of 60% to predict pre-eclampsia when using resistance index, and a sensitivity of 100% and a specificity of 66% when using unilateral or bilateral notches.

Women with kidney disease

One diagnostic study [EL = II] showed that uterine artery Doppler velocimetry at 19–24 weeks of gestation has a sensitivity of 50% and a specificity of 75% when using resistance index, and a sensitivity of 50% and a specificity of 79% when using albumin:creatinine ratio.

Women with mixed high-risk factors

Three diagnostic studies [EL = II] showed that uterine artery Doppler velocimetry at 22–24 weeks of gestation has a sensitivity of 78–97% and a specificity of 42–71%.

Prediction of intrauterine growth restriction

Women with previous pre-eclampsia

One diagnostic study [EL = II] showed that uterine artery Doppler velocimetry at 24 weeks of gestation has a sensitivity of 85% and a specificity of 70% to predict IUGR when using resistance index, and a sensitivity of 85% and a specificity of 77% when using unilateral or bilateral notches.

Women with kidney disease

One diagnostic study [EL = II] showed that uterine artery Doppler velocimetry at 19–24 weeks of gestation has a sensitivity of 83% and a specificity of 80% when using resistance index, and a sensitivity of 83% and a specificity of 84% when using albumin:creatinine ratio.

Women with mixed high-risk factors

One diagnostic study [EL = II] showed that uterine artery Doppler velocimetry at 22–24 weeks of gestation has a sensitivity of 84% and a specificity of 39%.

GDG interpretation of the evidence

The information on the predictive value of uterine artery Doppler velocimetry in women at high risk of pre-eclampsia is of poor quality and uses a variety of Doppler measurements and outcomes. The size of the individual studies is small.

Overall, the GDG feels that both the negative predictive ability and the sensitivity are not sufficiently reassuring to encourage clinicians to alter individual patient management in the group of women at high risk of pre-eclampsia based on normal or abnormal uterine artery Doppler velocimetry between 20 and 24 weeks. Given that this group of women is already advised to take aspirin, the GDG was uncertain which clinical intervention discrimination by uterine artery Doppler velocimetry would drive or would alter outcomes. The GDG has recommended further research in this area.

Table 8.1 Use of uterine artery Doppler velocimetry to predict pre-eclampsia or intrauterine growth restriction in women with previous pre-eclampsia or kidney disease

Study	Population demographic characteristics	Gestational age	Index	Parameter	Pre-eclampsia	IUGR	Notes
Previous pre-eclampsia							
Frusca *et al.* (1996), Italy[158]	*n* = 56 previous pre-eclampsia: 2 cases had had eclampsia, 24 cases had had early-onset pre-eclampsia (before 34 weeks of gestation), 17 had also had IUGR and 6 had also had intrauterine fetal demise	24 weeks	RI: abnormal > 0.58	Sensitivity: Specificity: PPV: NPV:	100% 60% 13% 100%	85% 70% 46% 94%	48 of the 56 women were on 50 mg aspirin, while 8 did not meet the criteria for prevention with low-dose aspirin because of late onset of previous pre-eclampsia Pre-eclampsia = diastolic blood pressure > 90 mmHg, proteinuria = > 300 mg/24 hours Endpoint: pre-eclampsia
Kidney disease							
Ferrier *et al.* (1994), New Zealand[159]	*n* = 51 with kidney disease (other than diabetic nephropathy)	19–24 weeks	RI: abnormal > 90th percentile	Sensitivity: Specificity: PPV: NPV	50% 75% 14% 95%	83% 80% 36% 97%	Renal function decreased if 2 out of the following 3 were abnormal: • plasma creatinine (≥90 micromol/litre) • plasma urea (≥6.5 mmol/litre) • creatinine clearance (≤1.5 ml/second). Reference: control group of 458 low-risk nulliparous women studied in the same period Endpoint: pre-eclampsia

NPV = negative predictive value; PPV = positive predictive value; RI = resistance index

Table 8.2 Use of uterine artery Doppler velocimetry to predict pre-eclampsia or intrauterine growth restriction in women with high-risk pregnancies

Study	Population demographic characteristics	Gestational age	Index	Parameter	Pre-eclampsia	IUGR	Notes
Parretti *et al.* (2003), Italy[76]	*n* = 144, previous pre-eclampsia (*n* = 87), previous stillbirth (*n* = 22), previous placental abruption (*n* = 11), previous IUGR (*n* = 24) Median age 34.5 years (range 27–41 years), gravidity 2 or 3, parity 1 or 2	24 weeks	RI: abnormal ≥0.58	Sensitivity: Specificity: PPV: NPV:	77.8% 67.6% 44.4% 90.1%	Not reported	Exclusion criteria: smoking, kidney disease, cardiovascular disease, diabetes, multiple pregnancy, fetal chromosomal abnormalities, or if already on low-dose aspirin Pre-eclampsia = blood pressure > 140/90 mmHg, proteinuria > 300 mg/24 hours Endpoint: pre-eclampsia
Caforio *et al.* (1999), Italy[77]	*n* = 335, chronic hypertension (*n* = 89), pre-eclampsia (*n* = 76), type 1 diabetes (*n* = 58), autoimmune disease (*n* = 53), systemic lupus erythematosus (*n* = 17), kidney disease (*n* = 34), previous stillbirth (*n* = 91), IUGR (*n* = 20) and recurrent miscarriage (*n* = 119) Mean age 31 ± 4.8 years	*n* = 249 at 22–24 weeks	RI: abnormal > 90th percentile	Sensitivity: Specificity: PPV: NPV:	97% 71% 31% 99%	77% 72% 37% 94% (Endpoint: birthweight < 1750 g)	Exclusion criteria: congenital defects, chromosomal abnormalities, multiple gestations, infections, Rhesus isoimmunisation, non-immune hydrops, prelabour rupture of the membranes, intrauterine deaths or delivery before 26 weeks of gestation Endpoint: pre-eclampsia
Coleman *et al.* (2000), New Zealand[78]	*n* = 116, chronic hypertension (*n* = 69), previous recurrent pre-eclampsia (*n* = 24), previous early-onset pre-eclampsia requiring delivery at or before 32 weeks (*n* = 25), previous placental abruption (*n* = 10), kidney disease (*n* = 40), systemic lupus erythematosus (*n* = 13), antiphospholipid syndrome (*n* = 5) Mean age 31 years (range 19–43 years), 31/116 were nulliparous and 18% smoked during pregnancy	22–24 weeks	RI: any abnormal > 0.58 Bilateral notch	Sensitivity: Specificity: PPV: NPV: Sensitivity: Specificity: PPV: NPV:	91% 42% 37% 92% 29% 86% 47% 74%	84% 39% 33% 87% 36% 89% 53% 79%	Exclusion criteria: multiple pregnancies and pregnancies with recognised fetal abnormalities. Endpoint: pre-eclampsia Data for Both RI > 0.58, any notch, and Any RI and any notch were also reported.

NPV = negative predictive value; PPV = positive predictive value; RI = resistance index

8.10 Fetal monitoring in women with previous pre-eclampsia

Clinical effectiveness

No studies relating to this specific group were identified.

GDG interpretation of the evidence

Women with previous pre-eclampsia, particularly those with severe disease or serious perinatal adverse outcomes, are at risk both of recurrent pre-eclampsia (see Chapter 10) and of IUGR. The GDG feels that limited routine surveillance of fetal growth is justified for these women.

Recommendations

In women with chronic hypertension, carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry between 28 and 30 weeks and between 32 and 34 weeks. If results are normal, do not repeat at more than 34 weeks, unless otherwise clinically indicated.

In women with chronic hypertension, only carry out cardiotocography if fetal activity is abnormal.

In women with mild or moderate gestational hypertension, carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry if diagnosis is confirmed at less than 34 weeks. If results are normal, do not repeat at more than 34 weeks, unless otherwise clinically indicated.

In women with mild or moderate gestational hypertension, do not carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry if diagnosis is confirmed after 34 weeks, unless otherwise clinically indicated.

In women with mild or moderate gestational hypertension, only carry out cardiotocography if fetal activity is abnormal.

Carry out cardiotocography at diagnosis of severe gestational hypertension or pre-eclampsia.

If conservative management of severe gestational hypertension or pre-eclampsia is planned carry out all the following tests at diagnosis:

- ultrasound fetal growth and amniotic fluid volume assessment.
- umbilical artery Doppler velocimetry.

If the results of all fetal monitoring are normal in women with severe gestational hypertension or pre-eclampsia, do not routinely repeat cardiotocography more than weekly.

In women with severe gestational hypertension or pre-eclampsia, repeat cardiotocography if any of the following occur:

- the woman reports a change in fetal movement
- vaginal bleeding
- abdominal pain
- deterioration in maternal condition.

In women with severe gestational hypertension or pre-eclampsia, do not routinely repeat ultrasound fetal growth and amniotic fluid volume assessment or umbilical artery Doppler velocimetry more than every 2 weeks.

If the results of any fetal monitoring in women with severe gestational hypertension or pre-eclampsia are abnormal, tell a consultant obstetrician.

For women with severe gestational hypertension or pre-eclampsia, write a care plan that includes all of the following:

- the timing and nature of future fetal monitoring
- fetal indications for birth and if and when corticosteroids should be given
- when discussion with neonatal paediatricians and obstetric anaesthetists should take place and what decisions should be made.

Carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry starting at between 28 and 30 weeks (or at least 2 weeks before previous gestational age of onset if earlier than 28 weeks) and repeating 4 weeks later in women with previous:

- severe pre-eclampsia
- pre-eclampsia that needed birth before 34 weeks
- pre-eclampsia with a baby whose birth weight was less than the 10th centile
- intrauterine death
- placental abruption.

In women who are at high risk of pre-eclampsia, only carry out cardiotocography if fetal activity is abnormal.

Research recommendation

Is uterine artery Doppler velocimetry of value in the clinical management of women at high risk of pre-eclampsia?

Why this is important

Uterine artery Doppler velocimetry is a poor predictor of pre-eclampsia as it has limited test accuracy. It is not clear how knowledge of uterine Doppler in women already identified at high risk of pre-eclampsia can influence clinical care or outcome. Studies in high risk women have involved small numbers and often mixed groups so that any benefit to a specific group could be masked.

Randomised trials of uterine artery Doppler should be carried out in women at high risk of pre-eclampsia (chronic hypertension, previous pre-eclampsia, antiphospholipid syndrome, kidney disease) and in women with multiple moderate risk factors. Trials should compare a policy of revealed uterine artery Doppler with unrevealed Doppler. Outcomes should be the consequences of severe pre-eclampsia including need for critical care, perinatal mortality and severe neonatal morbidity. Trials should be stratified for maternal risk factors.

9 Intrapartum care

9.1 Introduction

In 2007, NICE published guidance on intrapartum care for uncomplicated pregnancies.[28] Many of the routine aspects of care recommended in that guidance are applicable to every woman in labour. NICE also recommended that women with hypertensive disorders of pregnancy should be advised to give birth in a consultant-led labour ward.

This chapter has searched for evidence of areas where obstetric and midwifery care should differ from general recommended care if a woman has a hypertensive disorder. Medical care and care where severe disease is present are covered in Chapter 10.

The GDG identified the following areas of care that might need to carry different recommendations:

- frequency of blood pressure observations during labour
- haematological and biochemical monitoring
- care during epidural analgesia
- management of the second stage of labour
- management of the third stage of labour.

9.2 Blood pressure

Clinical effectiveness

No studies were identified.

GDG interpretation of the evidence

As in routine intrapartum care, there is no evidence to inform frequency of observations of maternal health. The GDG feels that there is no reason to alter the frequency of routine observations, with the exception of blood pressure. Because severe hypertension can develop from mild to moderate hypertension at any time in the course of labour, the GDG feels that this group of women should have their blood pressure measured at least hourly. Severe hypertension should be monitored continually. Women should continue previously prescribed antihypertensives during labour.

Recommendations

Women with hypertensive disorders during pregnancy should be given advice and treatment in line with 'Intrapartum care: management and delivery of care to women in labour' (NICE clinical guideline 55), unless it specifically differs from recommendations in this guideline.

During labour, measure blood pressure:

- hourly in women with mild or moderate hypertension
- continually in women with severe hypertension.

Continue use of antenatal antihypertensive treatment during labour.

9.3 Haematological and biochemical monitoring

Clinical effectiveness

For evidence, see Chapter 10 for severe disease and Chapters 6 and 7 for tests and frequency in the antenatal period. No other studies were found.

GDG interpretation of the evidence

There is no evidence to inform additional testing of women with hypertensive disorders who present in labour. The previously made recommendations for the antenatal period for the type of tests and their timing should also apply during labour (Chapters 6 and 7).

Recommendation

Determine the need for haematological and biochemical tests during labour in women with mild or moderate hypertension using the same criteria as in the antenatal period even if regional analgesia is being considered.

9.4 Care during epidural analgesia

Clinical effectiveness

Three RCTs were included.[161-163] All RCTs compared epidural with intravenous analgesia. However, the populations were different for each trial: hypertensive disorders during pregnancy[163] [EL = 1+], pre-eclampsia[162] [EL = 1−] and severe pre-eclampsia[161] [EL = 1+] (see Table 9.1).

Women with hypertensive disorders in pregnancy

An RCT from the USA compared the peripartum and perinatal effects of epidural with intravenous labour analgesia in 738 women with pregnancy-induced hypertension (diastolic blood pressure 90 mmHg or higher) who were admitted to labour (see Table 9.1 for the exclusion criteria).[163] [EL = 1+]

Women were randomly allocated, using a computer-generated random number table, to receive either epidural analgesia ($n = 372$) or intravenous analgesia ($n = 366$) (Table 9.1). Allocation was concealed using sealed numbered opaque envelopes that contained the treatment allocation. The envelopes were assigned and opened when the enrolled women requested relief of labour pain. Baseline characteristics of included women (age, height, weight and race) were comparable in the two groups except for a difference in the proportion of nulliparous women, more of whom were assigned to the patient-controlled intravenous analgesia group (242 of 372 versus 273 of 366; $P = 0.005$).

Women receiving epidural analgesia had statistically significantly longer second stage labour than those receiving intravenous analgesia (second stage: 53 ± 50 minutes versus 40 ± 42 minutes; $P = 0.002$). They were also more likely to develop intrapartum fever (76 of 372 versus 26 of 366: RR 2.88; 95% CI 1.89 to 4.38). The mean arterial pressure decrease after analgesia was higher in the epidural group (25 ± 18 mmHg versus 13 ± 14 mmHg; $P < 0.001$) and they were more likely to be given ephedrine to treat this hypotension (40 of 372 versus none of 366: RR 79.70; 95% CI 4.92 to 1291.32) and to receive intrapartum intravenous fluids (1525 ± 859 ml versus 954 ± 747 ml; $P < 0.001$).

Instrumental vaginal births (forceps) were statistically significantly higher in the epidural analgesia group (51 of 372 versus 27 of 366: RR 1.86; 95% CI 1.19 to 2.90). No statistically significant differences in spontaneous vaginal birth or caesarean section were found between the two groups. The need for oxytocin induction was higher in the intravenous group (100 of 372 versus 181 of 366: RR 0.54; 95% CI 0.45 to 0.66). However, no statistically significant difference was found in the need for oxytocin augmentation (152 of 372 versus 129 of 366: RR 1.16; 95% CI 0.96 to 1.40).

The neonatal outcomes of 5-minute Apgar scores (less than or equal to 3 and less than 7), admission to NICU and need for ventilation in the first 24 hours were similar in the groups. The number of babies with umbilical artery pH less than 7.0 or less than 7.1 was also similar in the groups. However, babies of women treated with intravenous analgesia were statistically significantly more likely to have umbilical artery pH less than 7.2 (21 of 372 versus 41 of 366: RR 0.50; 95% CI 0.30 to 0.84). They were also statistically significantly more likely to be given naloxone (two of 372 versus 40 of 366: RR 0.05; 95% CI 0.01 to 0.20).

Women with pre-eclampsia

An RCT from India assessed the use of labour epidural analgesia in 200 nulliparous women with pre-eclampsia (see Table 9.1 for the exclusion criteria).[161] [EL = 1−] Participants were randomly allocated by the 'rule of odds to even' into an epidural analgesia group ($n = 100$) and a no epidural analgesia group ($n = 100$). Concealment of allocation was unclear. The demographics of the subjects in both groups were comparable in terms of age, height, weight, BMI and gestational period.

The study showed no statistically significant difference in mode of delivery (normal vaginal, instrumental vaginal and caesarean section) between the two groups. Indications for instrumental delivery (fetal distress, prophylactic, non-progressive second stage) and indications for caesarean section (fetal distress, cephalopelvic disproportion, non-progressive first stage) were the same between the two groups. The incidence of a prolonged second stage of labour was not statistically significantly different between the groups (three of 100 versus one of 100: RR 3.00; 95% CI 0.32 to 28.36).

Neonatal outcomes were similar between the groups, including Apgar score less than 6 at 5 minutes (five of 100 versus seven of 100: RR 0.71; 95% CI 0.24 to 2.18) and the necessity of neonatal resuscitation (14 of 100 versus 13 of 100: RR 1.07; 95% CI 0.53 to 2.1).

Women with severe pre-eclampsia

An RCT from the USA investigated the relationship between intrapartum analgesia and the caesarean section rate in women with severe pre-eclampsia.[162] [EL = 1+] One hundred and sixteen women with severe pre-eclampsia who were in labour with a singleton pregnancy and vertex presentation were randomly allocated to an epidural analgesia group ($n = 56$) or an intravenous opioid analgesia group ($n = 60$). Computer-generated block randomisation was used, which was stratified according to gestational age less than 35 weeks versus 35 weeks or longer. Group assignments were sealed in consecutively numbered opaque envelopes (see Table 9.1 for the exclusion criteria). Baseline maternal demographics (age, weight, nulliparous, race, gestational age and initial cervical dilation) were comparable between the two groups.

The study showed no statistically significant differences in mode of delivery or indications for caesarean section between the two groups. The incidence of seizure, mechanical ventilation and oliguria were also similar. However, the mean intrapartum pain scores were statistically significantly lower (4 ± 3 versus 7 ± 3; $P < 0.001$) and the median postpartum satisfaction scores were statistically significantly higher in the epidural group (median 3 (range 1–4) versus median 2 (range 1–4); $P < 0.01$). There was also a trend towards a higher use of ephedrine in the epidural group but this did not reach statistically significant level (five of 56 versus none of 60: RR 11.77; 95% CI 0.67 to 208.14).

Babies from the intravenous opioid group received naloxone statistically significantly more often at the time of delivery (five of 56 versus 31 of 60: RR 0.17; 95% CI 0.07 to 0.41). Other neonatal outcomes were similar between the groups, including neonatal death (three of 56 versus none of 60: RR 7.49; 95% CI 0.40 to 141.87)) and admission to NICU (45 of 56 versus 44 of 60: RR 1.06; 95% CI 0.87 to 1.29). Similarly, the number of neonates with Apgar score less than 7 at 1 minute and at 5 minutes was not statistically signficantly different between the two groups.

Evidence statement

Gestational hypertension

An RCT [EL = 1+] that compared epidural with intravenous analgesia at labour in women with pregnancy-induced hypertension showed that women receiving epidural analgesia had

statistically significantly longer second stage labour (53 ± 50 minutes versus 40 ± 42 minutes; $P = 0.002$) and were more likely to develop intrapartum fever (76 of 372 versus 26 of 366: RR 2.88; 95% CI 1.89 to 4.38). The decrease in mean arterial pressure after analgesia was higher in the epidural group (25 ± 18 mmHg versus 13 ± 14 mmHg; $P < 0.001$). Women given epidural analgesia were more likely to be given ephedrine to treat hypotension (40 of 372 versus none of 366: RR 79.70; 95% CI 4.92 to 1291.32) and to receive intrapartum intravenous fluids (1525 ± 859 ml versus 954 ± 747 ml; $P < 0.001$).

Instrumental vaginal births (forceps) and need for oxytocin induction were statistically significantly higher in the epidural analgesia group (51 of 372 versus 27 of 366: RR 1.86; 95% CI 1.19 to 2.90 and 100 of 372 versus 181 of 366: RR 0.54; 95% CI 0.45 to 0.66, respectively).

Babies of women treated with intravenous analgesia were statistically significantly more likely to have umbilical artery pH less than 7.2 (21 of 372 versus 41 of 366: RR 0.50; 95% CI 0.30 to 0.84) and to require naloxone (two of 372 versus 40 of 366: RR 0.05; 95% CI 0.01 to 0.20). No statistically significant differences were found in other neonatal outcomes.

Pre-eclampsia

An RCT [EL = 1−] compared epidural analgesia with no epidural analgesia (intramuscular tramadol) in women with pre-eclampsia. It showed no statistically significant differences in mode of delivery, indications for caesarean section or indications for instrumental vaginal birth between the two groups. The incidence of a prolonged second stage of labour was not statistically significantly different between the groups. Neonatal outcomes were also similar between the groups.

Severe pre-eclampsia

An RCT [EL = 1+] investigated the relationship between intrapartum analgesia and the caesarean section rate in women with severe pre-eclampsia. Mean intrapartum pain scores were statistically significantly lower ($P < 0.001$) and median postpartum satisfaction scores were statistically significantly higher in the epidural group ($P < 0.01$). There was also a trend towards a greater use of ephedrine in the epidural group but this did not reach statistical significance (five of 56 versus none of 60: RR 11.77; 95% CI 0.67 to 208.14). Babies from the intravenous opioid group received naloxone statistically significantly more often at the time of delivery (RR 0.17; 95% CI 0.07 to 0.41).

The study showed no differences in other maternal (mode of delivery, seizure, mechanical ventilation and oliguria) or neonatal outcomes (neonatal death, admission to NICU and Apgar score less than 7 at 1 minute and 5 minutes).

GDG interpretation of the evidence

The evidence reviewed uses epidural local anaesthetic doses that are rarely currently used in UK practice. Even with different doses, the studies do not appear to demonstrate different effects of epidural analgesia in women with hypertensive disorders compared with the general obstetric population. The GDG's view is therefore that the presence of hypertensive disorders during pregnancy does not change the choice of analgesia during labour and that no alterations in the techniques of regional analgesia are needed.

The GDG considered that in women with severe pre-eclampsia, preloading and maintenance fluid infusion need not be administered routinely before establishing low-dose epidural analgesia and combined spinal epidural analgesia.

Recommendationon

Do not preload women who have severe pre-eclampsia with intravenous fluids before establishing low-dose epidural analgesia and combined spinal epidural analgesia.

Table 9.1 Use of epidural analgesia in women with hypertensive disorders during pregnancy

Study	Evidence level	*n*	Population	Exclusion criteria	Intervention: epidural analgesia	Comparison
Lucas et al. (2001)[163] USA	1+	738 (372, 366)	Pregnancy-induced hypertension (diastolic blood pressure ≥90 mmHg)	• Treated chronic hypertension • Prior analgesia/sedation • Contraindication to labour and/or vaginal delivery	Intravenous infusion of 500 ml of lactated Ringer's solution; then bolus (epidural injection) of 0.25% bupivacaine followed by a continuous epidural infusion (0.125% bupivacaine hydrochloride with 2 mg/ml[a] of fentanyl) (T10 sensory level)	Intravenous analgesia: Intravenous bolus 50 mg pethidine hydrochloride with 25 mg promethazine. Infusion pump was then used (maximum 15 mg pethidine hydrochloride every 10 minutes) if needed
Patel *et al.* (2005) [161] India	1–	200 (100, 100)	Nulliparous women with pre-eclampsia	• Maternal haemorrhage • Coagulopathy • Infection at the site of insertion of the needle • Advanced labour at admission (> 7cm dilation)	Intravenous infusion of 540 ml of lactated Ringer's solution; then bolus (epidural injection) of 8 ml bupivacaine hydrochloride 0.125% with tramadol 50 mg (T10 to L1 sensory level)	No epidural analgesia: intramuscular tramadol 50 mg for pain relief
Head *et al.* (2002)[162] USA	1+	116 (56, 60)	Severe pre-eclampsia (singleton; vertex; > 24 weeks; dilation < 5 cm)	• Platelet count < 80 × 10^9/litre • Pulmonary oedema • Non-reassuring fetal heart rate requiring imminent delivery • Abnormal airway examination that might predict an increased risk of difficult intubation	Intravenous infusion of 250–500 ml of lactated Ringer's solution; then bolus (epidural injection) of 3–5 ml of 0.25% bupivacaine followed by a continuous epidural infusion (0.125% bupivacaine with fentanyl 2 micrograms/ml at an initial rate of 10 ml/hour) (T10 sensory level)	Intravenous analgesia: pethidine hydrochloride via patient-controlled analgesia device. The self-administered dose was 10 mg, with a lock-out interval of 10 minutes (maximum dose: 240 mg every 4 hours)

[a] A fentanyl concentration of 2 mg/ml was reported by the authors but this appears to be a typographical error and should probably have been 2 micrograms/ml.

9.5 Management of the second stage of labour

Clinical effectiveness

No studies were identified that examined the clinical outcomes of different managements, including duration, of the second stage of labour.

GDG interpretation of the evidence

There is no evidence to guide clinical practice. Severe hypertension carries a risk of CVA and other cardiovascular complications. Fetal risks such as placental abruption might also increase in the presence of hypertension in pregnancy. These factors need to be taken into account in management of the second stage of labour. However, the GDG does not consider that the second stage of labour should routinely be shortened in women with stable mild or moderate hypertension. Consideration should be given to limiting the duration of the second stage of labour in women with severe hypertension that is unresponsive to initial treatment.

Recommendations

Do not routinely limit the duration of the second stage of labour:

- in women with stable mild or moderate hypertension or
- if blood pressure is controlled within target ranges in women with severe hypertension.

Recommend operative birth in the second stage of labour for women with severe hypertension whose hypertension has not responded to initial treatment.

9.6 Management of the third stage of labour

Clinical effectiveness

For evidence, see the NICE 'Intrapartum care' clinical guideline.[28]

GDG interpretation of the evidence

The GDG considers that the recommendation that oxytocin alone (without ergometrine) is the drug of choice for the routine active management of third stage of labour applies also to women with hypertensive disorders in pregnancy. The routine use of ergometrine should be avoided in this group of women because of its tendency to exacerbate hypertension. Other drugs, such as misoprostol, that have been studied in the third stage of labour also increase blood pressure more frequently than oxytocin.

There was, therefore, no recommendation relating to the third stage of labour that was any different to the recommendations already contained in the NICE intrapartum care guideline.

10 Medical management of severe hypertension or severe pre-eclampsia in a critical care setting

10.1 Introduction

Severe pre-eclampsia continues to cause maternal and perinatal morbidity. The UK Confidential Enquiries into Maternal Death have consistently reported substandard care in the management of these women. Protocols and guidelines have been developed in most units and more recently supported by guidance in this area from the Royal College of Obstetricians and Gynaecologists (RCOG). This section reviews the evidence for the acute management of severe pre-eclampsia that is conducted within a critical care setting, or what is more usually known as high-dependency care. In most circumstances, this occurs following a decision to end the pregnancy.

A single literature search was conducted for the various interventions: antihypertensive drugs, anticonvulsant drugs, steroids for HELLP syndrome (to prolong pregnancy) and for fetal lung maturation, fluid therapy and operative birth (caesarean section). The population studied was women with severe pre-eclampsia, eclampsia, severe hypertension or HELLP syndrome. The search identified 3379 references, of which 152 were retrieved.

10.2 Anticonvulsants

Clinical effectiveness

Six high-quality publications were identified.[164-169] [EL = 1++] Four of these were Cochrane systematic reviews[164-167] and the remaining two were separate publications that reported follow-up data from a single large double-blind RCT,[168;169] which was included in one of the Cochrane systematic reviews.[167] Of the Cochrane systematic reviews, one examined magnesium sulphate and other anticonvulsants for the prevention of eclampsia in women with pre-eclampsia,[167] and the other three compared magnesium sulphate with other anticonvulsants for the treatment of eclampsia.[164-166]

Prevention of eclampsia

Magnesium sulphate versus placebo or no treatment

A Cochrane systematic review[167] [EL = 1++] investigated the differential effects of magnesium sulphate (intramuscular or intravenous) when compared with placebo or no treatment for the care of women with pre-eclampsia. A subgroup analysis by severity of pre-eclampsia was also conducted: severe pre-eclampsia was defined as two or more signs or symptoms of imminent eclampsia, or blood pressure of 170/110 mmHg or higher and 3+ proteinuria, or, if on antihypertensive treatment, 150/110 mmHg or higher and 2+ proteinuria, or if the individual study authors described them as having severe pre-eclampsia. Those who did not meet any of the above criteria were classified as not having severe pre-eclampsia, which for the purpose of this guideline is reported as mild or moderate pre-eclampsia.

Six RCTs were included in the review ($n = 11\,444$ women). One multicentre RCT (the Magpie trial) involved 10 141 women. Other smaller trials were conducted in the USA, South Africa and

Taiwan. The quality of the studies included in this review ranged from excellent to poor. In the largest study, concealment of allocation was secure and completeness of follow-up was 99%. In one trial, the procedure used for trial entry did not give secure concealment of allocation and 17% of women were lost to follow-up. Apart from the Magpie trial, few studies attempted to blind administration of the allocated treatment.

Women with severe pre-eclampsia

In women with severe pre-eclampsia, magnesium sulphate was statistically significantly better than none/placebo in preventing eclampsia (three RCTs, $n = 3555$: RR 0.37; 95% CI 0.22 to 0.64). No statistically significant differences were found between the two groups in terms of maternal death, serious maternal morbidity, pulmonary oedema, placental abruption or kidney dialysis. The stillbirth and neonatal death rates were not statistically significantly different between the two groups.

Women with mild or moderate pre-eclampsia

Results for the mild or moderate pre-eclampsia subgroup showed that magnesium sulphate was statistically significantly better than none/placebo in preventing eclampsia (four RCTs, $n = 3889$: RR 0.44: CI 0.28 to 0.69). Other outcomes, however, were not statistically significantly different between the two groups (maternal death, serious maternal morbidity, stillbirth and neonatal death).

Follow-up for women (outcomes at 2 years)

A large RCT (the Magpie trial)[168] [EL = 1++] investigated the prognosis and possible unexpected adverse events related to the use of magnesium sulphate in the cohort of women with pre-eclampsia in the original trial.[170] In the Magpie trial, 7927 women with pre-eclampsia before birth or 24 hours postpartum (diastolic blood pressure 90 mmHg or higher, systolic blood pressure 140 mmHg or higher, proteinuria 1+ or more) were randomised to receive either magnesium sulphate (intravenous or intramuscular) or identical placebo regimens. Of the 4782 women contacted for the follow-up study, 3375 women participated (reasons for exclusions were the feasibility of following up in some centres, women discharged without a surviving child, and women who opted out of centres that contacted fewer than 20% of families). Women were randomised either via a central telephone service or consecutively numbered sealed treatment packs stratified by centre. A computer-generated allocation sequence was used. The baseline characteristics of the women in the two groups at trial entry were comparable.

The primary outcome reported was death or serious morbidity related to pre-eclampsia. No statistically significant difference in the primary outcome was found between the two groups (58 of 1650 versus 72 of 1725: RR 0.84; 95% CI 0.60 to 1.18). This difference remained non-statistically significant when 'death' and 'serious morbidity' outcomes were analysed separately. Subgroup analyses were conducted for the primary outcome to see whether the results were affected by the severity of pre-eclampsia (severe versus mild–moderate), the randomisation (before delivery versus after delivery) or the respective country's perinatal mortality index (high, middle or low). Results were consistent across all subgroups.

The only outcomes for which the difference between the magnesium sulphate and placebo groups achieved statistical significance was gynaecological problems, for which the risk was higher in the magnesium group (RR 1.59; 95% CI 1.17 to 2.16).

Follow-up for children (outcomes at 18 months)

In another publication[169] [EL = 1++] from the Magpie trial, the authors investigated whether giving magnesium sulphate to women with pre-eclampsia had effects on the child's chance of developing major neurosensory disability (18 months follow-up). This follow-up study contacted 4483 children, of whom 3283 ultimately participated (reasons for exclusion were those not eligible for follow-up, or those born at centres where follow-up was not thought possible).

The primary outcome reported was death or non-congenital neurosensory disability. No statistically significant difference in the primary outcome was found between babies born to mothers treated with magnesium sulphate and those born to mothers treated with placebo (245 of 1635 versus 233 of 1648: RR 1.10; 95% CI 0.93 to 1.29). The difference remained non-statistically significant when 'death' and 'neurosensory disability' outcomes were analysed separately (death: 226 of 1635 versus 206 of 1648: RR 1.06; 95% CI 0.90 to 1.25; neurosensory disability: ten of 1409 versus 27 of 1442: RR 0.72; 95% CI 0.40 to 1.29).

Subgroup analyses were conducted for the primary outcome to see whether the results were affected by the severity of pre-eclampsia at trial entry (severe, moderate, mild), gestation at birth (up to 33 weeks, more than 33 weeks) or the country's perinatal mortality index (high, middle, low).). Results were consistent across all subgroups.

No statistically significant differences were found between the two groups in terms of having isolated speech delay or other significant disability.

Cost effectiveness

A literature search identified 100 studies and four were ordered. Only one study[171] met the inclusion criteria. The study was a multinational trial-based economic evaluation of the Magpie trial. Outcome and hospital resource use data were available for the trial period from the 33 participating countries. The study was an international study coordinated from the UK. The GDG believes that the study represented practice that was relevant to the UK. Country-specific unit costs were collected as part of the study and converted into USD at 2001 prices using national consumer price indices. The conversion of the reported CPI in USD at 2001 to prices in GBP 2009 was done using a CPI conversion calculator.[172] Cost effectiveness was estimated for three categories of country grouped by gross national income (GNI) into high-, middle- and low-GNI countries using a regression model. Uncertainty was explored using probabilistic sensitivity analysis. Results of the high-income countries that are relevant to the UK were abstracted.

Using magnesium sulphate to prevent eclampsia in women with pre-eclampsia costs, on average, $86 (approximately £60) and results in reductions in hospital resource use, due to the lower risk of eclampsia, worth an average of $20 (approximately £14) per woman. Because overall the reduction in healthcare expenditure per pregnancy is less than the cost of the magnesium sulphate treatment, the net health service cost is higher for the intervention group than for the control group. Thus the incremental healthcare cost to prevent a case of eclampsia is $21,202 (approximately £14,752).

The cost-effectiveness acceptability curves show the probability of prophylactic magnesium sulphate being cost effective as a function of the decision-maker's willingness to pay to prevent a case of eclampsia against the alternative of not providing prophylactic anticonvulsant. Eighty percent certainty about the cost effectiveness of the intervention was not reached, even if decision-makers would be willing to pay more than $50,000 (approximately £34,800) per case of eclampsia prevented. A subgroup analysis by severity of pre-eclampsia showed that it would approximately halve the cost per case of eclampsia prevented since the absolute benefit from treatment is huge. The estimated ICER would fall to $11,149; (approximately £7,760) (95% CI £500 to £59,200).

The authors concluded that magnesium sulphate for pre-eclampsia is cost effective in the prevention of eclampsia in high-GNI countries. Cost effectiveness substantially improves if it is used only for severe pre-eclampsia. This was a well-conducted economic analysis with results that were well presented. Although NICE's preferred measure of outcome is a QALY, the study did not consider this; however, the GDG believes this approach would be unlikely to change the conclusions of the analysis since eclampsia is a good proxy for both the quality and the quantity of life that would generate the QALYs.

Evidence statement

A Cochrane review [EL = 1++] showed that in women with either severe or mild/moderate pre-eclampsia, magnesium sulphate was statistically significantly better than no treatment/placebo in preventing eclampsia. However, there were no statistically significant differences in other outcomes, including maternal death and serious maternal morbidity.

A well-conducted economic analysis found that magnesium sulphate was cost effective in preventing eclampsia when compared with placebo in women with pre-eclampsia. The cost effectiveness improved with severity of pre-eclampsia.

A large RCT [EL = 1++] investigated the long-term effects of magnesium sulphate used in pre-eclampsia in the mothers (at 2 years follow-up) and their babies (at 18 months follow-up) in comparison with placebo. The trial found no statistically significant differences between the

mothers or the babies of the two groups in the primary outcomes studied (mothers: death or serious morbidity potentially related to pre-eclampsia; babies: death or non-congenital neurosensory disability). Subgroup analysis by severity of pre-eclampsia was consistent across all subgroups. The only outcome for which the difference between the two groups of mothers achieved statistical significance was 'gynaecological problems', for which the risk was higher in the magnesium sulphate group. No statistically significant differences were found in the babies for any of the other studied outcomes (isolated speech delay or significant disability).

Clinical effectiveness

Treatment of eclampsia

Three Cochrane systematic reviews studied the use of magnesium sulphate in women with eclampsia compared with diazepam,[164], phenytoin[165] and lytic cocktail[166] (lytic cocktail is no longer used in UK clinical practice). For a better overview of the available evidence, results for the primary outcomes of these reviews are presented in Tables 10.1a (maternal outcomes) and 10.1b (fetal outcomes).

Magnesium sulphate versus diazepam

A Cochrane systematic review investigated the effects of magnesium sulphate (intramuscular or intravenous) compared with diazepam.[164] [EL = 1++] Participants were women with eclampsia at trial entry before or after delivery, who had singleton or multiple pregnancies, and who may have had an anticonvulsant before trial entry.

Seven RCTs were included in the review ($n = 1441$ women). Most trials included women with both antepartum and postpartum eclampsia. Overall, about half the women in this review had also had an anticonvulsant before trial entry. The treatment regimens all included a loading dose and maintenance therapy. Three trials were of good quality; adequacy of concealment of allocation was unclear in four other trials. The largest contribution to the Cochrane systematic review was from a good-quality RCT (the Collaborative Eclampsia Trial),[173] which contributed 910 of the 1441 women in the review (63%). One study was available only as an unpublished report; another study was available as an abstract and an unpublished report. None of the trials could include blinding after randomisation because of the type of intervention.

Magnesium sulphate showed better results than diazepam in women with eclampsia. Both 'maternal death' and 'recurrence of convulsions' outcomes were statistically significantly less likely in the magnesium sulphate group compared with the diazepam group (maternal death: six RCTs, $n = 1336$; RR 0.59; 95% CI 0.37 to 0.94; recurrence of convulsions: seven RCTs, $n = 1441$; RR 0.44; 95% CI 0.34 to 0.57).

Babies of women treated with magnesium sulphate were statistically significantly less likely to stay in neonatal care (variously reported in the primary studies as NICU or special care baby unit (SCBU)) for longer than 7 days (three RCTs, $n = 631$; RR 0.66; 95% CI 0.46 to 0.95) and to be intubated at place of birth (two RCTs, $n = 591$; RR 0.67; 95% CI 0.45 to 1.00) when compared with babies born to mothers treated with diazepam. Besides, magnesium sulphate babies were statistically significantly less likely to score less than 7 in Apgar scale measured at both 1 minute (two RCTs, $n = 597$; RR 0.75; 95% CI 0.65 to 0.87) and 5 minutes after delivery (two RCTs, $n = 597$; RR 0.72; 95% CI 0.55 to 0.94).

Magnesium sulphate versus phenytoin

A Cochrane systematic review investigated the effects of magnesium sulphate (intramuscular or intravenous) compared with phenytoin.[165] [EL = 1++] Participants were women with eclampsia at trial entry either before or after delivery, who had singleton or multiple pregnancies, and who may have had an anticonvulsant before trial entry.

Six RCTs were included in the review ($n = 897$) which mainly comprised women with antepartum eclampsia (only 17% were postpartum). About 80% of the women had received an anticonvulsant before trial entry. Five trials were small, and one was large (the Collaborative Eclampsia Trial).[173] The Collaborative Eclampsia Trial contributed 777 of the 897 women in the Cochrane systematic review (87%). The methodological quality of the Collaborative Eclampsia Trial was good but concealment of allocation in the small trials was not adequate or not reported clearly. None of the trials could include blinding after randomisation because of the type of intervention.

The recurrence of convulsions was statistically significantly less likely in the magnesium sulphate group compared with the phenytoin group (five RCTs, $n = 895$; RR 0.31; 95% CI 0.20 to 0.47). Women in the magnesium sulphate group were statistically significantly less likely to be admitted to intensive care units (one RCT, $n = 775$; RR 0.67; 95% CI 0.50 to 0.89). They were also statistically significantly less likely to be given supportive mechanical ventilation (one RCT, $n = 775$; RR 0.66; 95% CI 0.49 to 0.90).

Babies born to women treated with magnesium sulphate were statistically significantly less likely to be admitted to NICU (one RCT, $n = 518$; RR 0.73; 95% CI 0.58 to 0.91) and were statistically significantly less likely to either die or to be admitted to NICU for more than 7 days (composite outcome of one RCT, $n = 518$; RR 0.53; 95% CI 0.33 to 0.86). Furthermore, fewer babies born to women treated with magnesium sulphate compared with babies born to women treated with phenytoin scored less than 7 in Apgar at 1 minute (one RCT, $n = 518$; RR 0.78; 95% CI 0.66 to 0.93). However, the Apgar score less than 7 at 5 minutes did not show a statistically significant difference.

Magnesium sulphate versus lytic cocktail

A Cochrane systematic review investigated the differential effects of magnesium sulphate (intramuscular or intravenous) compared with any combination of drugs known as 'lytic cocktail' regardless of their constituents or how they were administered.[166] [EL = 1++] Participants were women who had eclampsia at trial entry, which could have been before or after delivery, who had singleton or multiple pregnancies, and who may have had an anticonvulsant before trial entry.

Two RCTs were included in the review ($n = 199$ women). For one study, the randomisation procedure was described, although it is unclear whether there was any central record of the envelopes or whether the envelopes were to be used in a particular sequence. One woman with uncertain diagnosis was excluded from the analysis. The other study was only available as an abstract, and there was no information about concealment of allocation or how outcome was assessed. Some additional information about the interventions and outcomes for this study was obtained by recording data from the poster presentation. The lytic cocktail in both trials was a combination of pethidine, promethazine and chlorpromazine.

The recurrence of convulsions was statistically significantly less likely in the magnesium sulphate group compared with the phenytoin group (two RCTs, $n = 198$; RR 0.09; 95% CI 0.03 to 0.24). Women in the magnesium sulphate group had statistically significantly fewer cases of coma at more than 24 hours (one RCT, $n = 108$; RR 0.04; 95% CI 0.00 to 0.74) and of respiratory depression (two RCTs, $n = 198$; RR 0.12; 95% CI 0.02 to 0.91). Fetal or infant deaths were statistically significantly lower in the magnesium sulphate group (two RCTs, $n = 177$; RR 0.45; 95% CI 0.26 to 0.79).

Evidence statement

A Cochrane review [EL = 1++] showed that in women with eclampsia, magnesium sulphate had statistically significantly better results than diazepam in preventing maternal death and recurrence of convulsions. Babies of women treated with magnesium sulphate were statistically significantly less likely to stay in neonatal care (variously reported in the primary studies as NICU or SCBU) for more than 7 days, to be intubated at place of birth or have an Apgar score less than 7 at both 1 minute and 5 minutes from delivery.

A Cochrane review [EL = 1++] showed that in women with eclampsia, magnesium sulphate has statistically significantly better results than phenytoin in preventing recurrence of convulsions. They were also statistically significantly less likely to be admitted to ICU or to be given supportive mechanical ventilation. No statistically significant results were found between the two groups in preventing maternal death. Babies born to women treated with magnesium sulphate were statistically significantly less likely to be admitted to neonatal care (variously reported in the primary studies as NICU or SCBU), to stay there for more than 7 days or to die there after > 7 days.

A Cochrane review [EL = 1++] showed that in women with eclampsia, magnesium sulphate has statistically significantly better results than a cocktail of lytic agents in preventing recurrence of convulsions, having a coma after more than 24 hours or having respiratory depression. Fetal or infant deaths were statistically significantly lower in the magnesium sulphate group.

GDG interpretation of the evidence

The evidence supported the use of magnesium sulphate in severe pre-eclampsia to prevent progression to eclampsia, as the number needed to treat to prevent one eclamptic fit was 50, whereas in women who have pre-eclampsia with mild or moderate hypertension, 100 women would need to be treated to avoid an eclamptic fit. There was no difference for the mother or fetus in other outcome measures. Regarding recurrence, there was clear evidence from RCTs and systematic reviews that magnesium sulphate treatment in eclampsia reduces the incidence of further eclamptic fits. There was also clear evidence from systematic reviews that magnesium sulphate is more effective than phenytoin, diazepam and lytic cocktail in preventing further eclamptic fits (lytic cocktail is no longer relevant to UK clinical practice). The GDG's view is that treatment with magnesium sulphate is likely to be cost effective: it is cheaper and easier to administer than phenytoin, and it requires less follow-up nursing care than diazepam, which has sedative effects.[173] The GDG's view is that the regimen for administration of magnesium sulphate should be the intravenous regimen used in the Collaborative Eclampsia Trial,[173] because this trial contributed much of the evidence for the effectiveness of magnesium sulphate and was of better methodological quality than the other included studies. The intravenous regimen used in the Collaborative Eclampsia Trial[173] was:

- a loading dose of 4 g given intravenously over 5 minutes, followed by an infusion of 1 g/hour maintained for 24 hours
- recurrent seizures should be treated with a further dose of 2–4 g given over 5 minutes.

Most trials that compared the effectiveness of magnesium sulphate with phenytoin or diazepam also involved monitoring of respiration rate, urine output and tendon reflexes, but not serum, in women undergoing treatment.[164;165]

Recommendations

If a woman in a critical care setting who has severe hypertension or severe pre-eclampsia has or previously had an eclamptic fit, give intravenous magnesium sulphate.*

Consider giving intravenous magnesium sulphate* to women with severe pre-eclampsia who are in a critical care setting if birth is planned within 24 hours.

If considering magnesium sulphate* treatment, use the following as features of severe pre-eclampsia:

- severe hypertension and proteinuria **or**
- mild or moderate hypertension and proteinuria with one or more of the following:
  - symptoms of severe headache
  - problems with vision, such as blurring or flashing before the eyes
  - severe pain just below the ribs or vomiting
  - papilloedema
  - signs of clonus (≥ 3 beats)
  - liver tenderness
  - HELLP syndrome
  - platelet count falling to below 100×10^9 per litre
  - abnormal liver enzymes (ALT or AST rising to above 70 IU/litre).

Use the Collaborative Eclampsia Trial§ regimen for administration of magnesium sulphate:*

- loading dose of 4 g should be given intravenously over 5 minutes, followed by an infusion of 1 g/hour maintained for 24 hours
- recurrent seizures should be treated with a further dose of 2–4 g given over 5 minutes.

Do not use diazepam, phenytoin or lytic cocktail as an alternative to magnesium sulphate* in women with eclampsia.

* In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

§ The Eclampsia Trial Collaborative Group (1995) Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 345:1455–63.

Table 10.1a Maternal outcomes reported in systematic reviews of treatment for women with eclampsia – magnesium sulphate compared with diazepam, phenytoin and lytic cocktail (reported as RRs with 95% CIs)

Study	Maternal death	Recurrence of convulsions	Admission to ICU	Coma > 24 hours	Respiratory depression	Pulmonary oedema	Pneumonia	Mechanical ventilation	Kidney failure	CVA	HELLP syndrome	Placental abruption	Cardiac arrest
Magnesium sulphate versus diazepam													
Cochrane review[164] 7 RCTs, *n* = 1441 [EL = 1++]	6 RCTs, *n* = 1336: RR 0.59 (0.37–0.94)	7 RCTs, *n* = 1441: RR 0.44 (0.34–0.57)	2 RCTs, *n* = 974: RR 0.80 (0.60–1.08)	–	3 RCTs, *n* = 1025: RR 0.86 (0.57–1.30)	2 RCTs, *n* = 974: RR 0.99 (0.39–2.55)	4 RCTs, *n* = 1125: RR 0.64 (0.31–1.33)	3 RCTs, *n* = 1025: RR 0.73 (0.45–1.18)	4 RCTs, *n* = 1125: RR 0.87 (0.54–1.39)	3 RCTs, *n* = 1025: RR 0.64 (I0.33–1.23)	–	–	3 RCTs, *n* = 1025: RR 0.94 (0.47–1.88)
Magnesium sulphate versus phenytoin													
Cochrane review[165] 6 RCTs, *n* = 897 [EL = 1++]	2 RCTs, *n* = 797: RR 0.50 (0.24–1.05)	5 RCTs, *n* = 895: RR 0.31 (0.20–0.47)	1 RCTs, *n* = 775: RR 0.67 (0.50–0.89)	–	1 RCTs, *n* = 775: RR 0.71 (0.46–1.09)	2 RCTs, *n* = 825: RR 1.00 (0.47–2.10)	1 RCT, *n* = 775: RR 0.44 (0.24–0.79)	1 RCT, *n* = 775: RR 0.66 (0.49–0.90)	2 RCTs, *n* = 825: RR 1.48 (0.94–2.32)	1 RCTs, *n* = 775: RR 0.54 (0.20–1.46)	–	–	1 RCT, *n* = 775: RR 1.16 (0.39–3.43)
Magnesium sulphate versus lytic cocktail													
Cochrane review[166] 2 RCTs, *n* = 199 [EL = 1++]	–	2 RCTs, *n* = 198: RR 0.09 (0.03–0.24)	–	1 RCT, *n* = 108: RR 0.04 (0.00–0.74)	2 RCTs, *n* = 198: RR 0.12 (0.02–0.91)	–	1 RCT, *n* = 108: RR 0.10 (0.01–0.76)	1 RCT, *n* = 90: RR 0.20 (0.01–4.05)	1 RCT, *n* = 108: RR 0.22 (0.01–4.54)	1 RCT, *n* = 108: RR 0.22 (0.01–4.54)	1 RCT, *n* = 108: RR 3.35 (0.14–80.36)	1 RCT, *n* = 108: RR 0.84 (0.20–3.57)	1RCT, *n* = 108: RR 0.22 (0.01–4.54)

CVA = cerebrovascular accident; HELLP = haemolysis, elevated liver enzymes and low platelet count; ICU = intensive care unit

Shaded cells indicate statistically significant effects (at the 5% level)

Table10.1b Fetal outcomes reported in systematic reviews of treatment for women with eclampsia – magnesium sulphate compared with diazepam, phenytoin and lytic cocktail (reported as RRs with 95% CIs)

Evidence	Death of fetus or infant			Utilisation of neonatal care[a]		Death in neonatal care[a] > 7 days	Intubation at place of birth	Apgar score	
	Stillbirth	Perinatal death	Neonatal death	Admission	Stay > 7 days			< 7 at 1 minute	< 7 at 5 minutes
Magnesium sulphate versus diazepam									
Cochrane review[164] 7 RCTs, *n* = 1441 [EL = 1++]	4 RCTs, *n* = 756: RR 0.89 (0.63–1.26)	3 RCTs, *n* = 745: RR 1.04 (0.80–1.36)	3 RCTs, *n* = 716: RR 1.34 (0.84–2.14)	3 RCTs, *n* = 631: RR 0.90 (0.78–1.04)	3 RCTs, *n* = 631: RR 0.66, (0.46–0.95)	2 RCTs, *n* = 718: RR 0.95 (0.77–1.16)	2 RCTs, *n* = 591: RR 0.67 (0.45–1.00)	2 RCTs, *n* = 597: RR 0.75 (0.65–0.87)	2 RCTs, *n* = 597: RR 0.72, (0.55–0.94)
Magnesium sulphate versus phenytoin									
Cochrane review[165] 6 RCTs, *n* = 897 [EL = 1++]	2 RCTs, *n* = 665: RR 0.83 (0.61–1.13)	2 RCTs,*n* = 665: RR 0.85 (0.67–1.09)	2 RCTs, *n* = 665: RR 0.95 (0.59–1.53)	1 RCT, *n* = 518: RR 0.73 (0.58–0.91)	1 RCT, *n* = 518: RR 0.53 (0.33–0.86)	1 RCT, *n* = 643: RR 0.77 (0.63–0.95)	–	1 RCT, *n* = 518: RR 0.78 (0.66–0.93)	1 RCT, *n* = 518: RR 0.86, (0.52–1.43)
Magnesium sulphate versus lytic cocktail									
Cochrane review[166] 2 RCTs, *n* = 199 [EL = 1++]	2 RCTs, *n* = 177: RR 0.55 (0.26–1.16)	Fetal or infant death: 2 RCTs, *n* = 177: RR 0.45 (0.26–0.79)	2 RCTs *n* = 183: RR 0.39 (0.14–1.06)	–	–	–	–	–	–

[a] Neonatal care was variously reported in the primary studies as neonatal intensive care unit (NICU) or special care baby unit (SCBU)

Shaded cells indicate statistically significant effects (at the 5% level)

10.3 Antihypertensives

Clinical effectiveness

The population considered here included women with severe hypertension. No separate analyses were done for women with severe pre-eclampsia, severe chronic hypertension or chronic hypertension with superimposed pre-eclampsia. Eight studies were identified that compared various antihypertensive agents.[174-181]

One of these studies was a Cochrane systematic review[174] [EL = 1++] of all randomised trials (quasi-randomised designs were excluded) that looked at any comparison of one antihypertensive agent with another regardless of dose, route of administration or duration of therapy. Comparisons of alternative regimens of the same agent and of alternative agents within the same class of drug were not included. Participants were women with severe hypertension (diastolic blood pressure of 105 mmHg or higher and/or systolic blood pressure of 160 mmHg or higher) during pregnancy requiring immediate treatment. Postpartum women were excluded.

The overall number of RCTs included was 24 ($n = 2949$ women). All trials were small, apart from one ($n = 1750$) that compared nimodipine with magnesium sulphate.

The antihypertensive drugs evaluated in these trials were hydralazine, calcium-channel blockers (nifedipine, nimodipine, nicardipine and isradipine), labetalol, methyldopa, diazoxide, epoprostenol, ketanserin, urapidil, magnesium sulphate, prazosin and isosorbide. Most drugs were given either intravenously or intramuscularly, except nifedipine, nimodipine, isosorbide and prazosin, which were given orally. Dosage varied considerably between studies, in both amount and duration.

Most of the included trials were small. Only three studies recruited more than 100 women. Several trials were conducted in countries where English is not widely used. Only five trials ($n = 314$ women) had adequate concealment of allocation. Most of the others did not give adequate information about how or whether the allocation to treatment group was concealed. For most trials, the identity of the allocated drug could only be blinded after trial entry with use of a double placebo. This was stated to have been conducted in one study (50 women). In another two, the comparison was stated to have been blinded.

The review identified 12 different comparisons:

- hydralazine versus labetalol, calcium-channel blockers, ketanserin, urapidil or epoprostenol
- labetalol versus methyldopa, calcium-channel blockers or diazoxide
- magnesium sulphate versus nitrates or nimodipine
- nifedipine versus chlorpromazine.

Six other trials were identified that were not included in the Cochrane review – four[176;179-181] were EL = 1+ and two[177;178] were EL = 1–. These trials studied five comparisons:

- labetalol versus hydralazine
- calcium-channel blockers versus hydralazine
- diazoxide versus hydralazine
- nifedipine versus labetalol
- nifedipine versus nitroglycerine.

There is another well-conducted meta-analysis of RCTs[175] [EL = 1++] that compared hydralazine with other antihypertensive drugs in pregnant women with moderate to severe hypertension (moderate: diastolic blood pressure of 100–109 mmHg; severe: diastolic blood pressure of 110 mmHg or higher). Twenty-one RCTs were included ($n = 1085$ women). The randomisation method was adequate in 11 trials while it was unknown or inadequate in the other trials. Blinding was applied in four trials. The other 17 were either not blinded (11 trials) or blinding was not reported (six trials). Five of these studies had women with moderate hypertension (one trial, $n = 30$: labetalol versus hydralazine; two trials, $n = 59$: urapidil versus hydralazine; two trials, $n = 100$: ketanserin versus hydralazine).

The meta-analysis identified five comparisons (labetalol, calcium-channel blockers, ketanserin, urapidil or epoprostenol versus hydralazine). There is an overlap in the included trials with the

above-mentioned Cochrane review. However, the adverse effects and persistent high blood pressure outcomes were reported in more detail in this meta-analysis.

Overall, there were 15 different comparisons between a variety of antihypertensive drugs. Table 10.2 provides an overview of all the available evidence. Results for the primary outcomes of all included studies are presented in Tables 10.3 to 10.10. These tables present comparisons based on evidence available from two or more difference sources (the Cochrane systematic review, the meta-analysis or additional individual trials).

Table 10.10 presents comparisons based on evidence available in one source only (i.e. individual RCTs).

Labetalol versus hydralazine

The Cochrane review[174] [EL = 1++] included three RCTs ($n = 69$) that compared labetalol with hydralazine. No statistically significant differences were found between the two drugs.

The meta-analysis[175] [EL = 1++] included five RCTs ($n = 156$) that compared labetalol with hydralazine. Women treated with labetalol were statistically significantly more likely to have persistent high blood pressure in comparison with those treated with hydralazine (four RCTs, $n = 126$: RR 3.4; 95% CI 1.0 to 12.5). However, they were less likely to have hypotension (four RCTs, $n = 122$: RR 0.2; 95% CI 0.0 to 0.9) or to suffer from side effects (five RCTs, $n = 156$: RR 0.3; 95% CI 0.2 to 0.6).

A non-blinded randomised trial from Panama[176] [EL = 1+] that compared labetalol with hydralazine included 200 women (100 in each arm) with severe hypertension (blood pressure of 160/110 mmHg or higher), at 24 weeks of gestation or later with no concurrent antihypertensive therapy. Labetalol was given intravenously: 20 mg bolus, followed by 40 mg if not effective within 20 minutes, followed by 80 mg every 20 minutes up to a maximum dose of 300 mg (five doses). Hydralazine was given intravenously: 5 mg slow bolus and repeated every 20 minutes up to a maximum of five doses. The study showed no statistically significant differences between the two drugs either in the effectiveness of hypertension control or in the appearance of adverse effects.

Calcium-channel blockers versus hydralazine

The Cochrane review[174] [EL = 1++] included six RCTs ($n = 313$) that compared calcium-channel blockers with hydralazine. Women treated with calcium-channel blockers were statistically significantly less likely to have persistent high blood pressure than those treated with hydralazine (five RCTs, $n = 263$: RR 0.33; 95% CI 0.15 to 0.70). No other statistically significant differences were found.

The meta-analysis[175] [EL = 1++] included nine RCTs ($n = 619$) that compared calcium-channel blockers with hydralazine. Babies born to women treated with calcium-channel blockers were statistically significantly less likely to have fetal heart rate decelerations than those born to women treated with hydralazine (six RCTs, $n = 360$: RR 0.2; 95% CI 0.1 to 0.6). No other statistically significant differences were found.

Nifedipine versus hydralazine

A non-blinded quasi-randomised trial[177] [EL = 1−] from Ghana compared nifedipine with hydralazine. Women were numbered as they attended, with odd-numbered women joining the nifedipine group and even-numbered women joining the hydralazine group. The study included 79 women with severe pre-eclampsia (blood pressure of 160/110 mmHg or higher and proteinuria 1+ or more) who were at 28 weeks of gestation or later. Nifedipine was given sublingually (10 mg capsule) to 49 women. This was repeated every 30 minutes if blood pressure remained above 160/110 mmHg. After that, 10 mg tablets were given orally every 6–8 hours until delivery. Hydralazine was given intravenously (5 mg bolus) and was repeated at intervals determined by blood pressure measurements. When diastolic pressure stabilised at around 90–100 mmHg, 20–80 mg hydralazine tablets in divided doses were administered until delivery. The study showed that women on nifedipine were statistically significantly less likely to develop persistent high blood pressure than women treated with hydralazine (RR 0.28; 95% CI 0.11 to 0.71). No other statistically significant results were found.

Isradipine versus hydralazine

A small non-blinded quasi-randomised trial[178] [EL = 1 –] from Jamaica included 39 women with severe pre-eclampsia (blood pressure of 160/110 mmHg or higher, proteinuria 1+ or more) who were at 28 weeks of gestation or later. Isradipine was infused at 0.15 g/kg per minute* over 6 hours to a total maximum dose of 2.8 mg for 20 women. When diastolic pressure was controlled below 100 mmHg, slow-release tablets were started (5 mg, twice a day). Hydralazine was infused at 2 mg/kg/hour to a maximum dose of 20 mg, followed by oral alpha-methyldopa 500 mg three times a day for 19 women. The study only reported one outcome, caesarean section, which showed no statistically significant difference between the two groups.

Ketanserin versus hydralazine

The Cochrane review[174] [EL = 1++] included four RCTs ($n = 200$) that compared ketanserin with hydralazine. Women treated with ketanserin were statistically significantly more likely to have persistent high blood pressure than those treated with hydralazine (three RCTs, $n = 180$: RR 4.79; 95% CI 1.95 to 11.73). However, they were statistically significantly less likely to suffer adverse effects from the drug (three RCTs, $n = 120$: RR 0.32; 95% CI 0.19 to 0.53) or to develop HELLP syndrome (one RCT, $n = 44$: RR 0.20; 95% CI 0.05 to 0.81). No other statistically significant differences were found.

The meta-analysis[175] [EL = 1++] included four RCTs ($n = 190$) that compared ketanserin with hydralazine. Women treated with ketanserin were statistically significantly less likely to suffer from adverse effects than those treated with hydralazine (two RCTs, $n = 64$: RR 0.4; 95% CI 0.2 to 0.7). No other statistically significant differences were found.

Urapidil versus hydralazine

The Cochrane review[174] [EL = 1++] included two RCTs ($n = 59$) that compared urapidil with hydralazine. No statistically significant differences were found.

The meta-analysis[175] [EL = 1++] included two RCTs ($n = 59$) that compared urapidil with hydralazine. No statistically significant differences were found.

Epoprostenol versus hydralazine

The Cochrane review[174] [EL = 1++] included one RCT ($n = 47$) that compared epoprostenol with hydralazine. No statistically significant differences were found.

The meta-analysis[175] [EL = 1++] included one RCT ($n = 47$) that compared epoprostenol with hydralazine. No statistically significant differences were found.

Labetalol versus calcium-channel blockers

The Cochrane review[174] [EL = 1++] included one RCT ($n = 60$) that compared labetalol with nicardipine. No statistically significant differences were found.

A double-blind RCT[179] [EL = 1+] ($n = 50$) from the USA compared labetalol with nifedpine ($n = 25$ in each group). Women at 24 weeks of gestation of later with severe pre-eclampsia or chronic hypertension with superimposed pre-eclampsia, either intrapartum ($n = 29$) or within 24 hours postpartum ($n = 21$), were included. Severe hypertension was defined as sustained systolic blood pressure of 170 mmHg or higher or diastolic blood pressure of 105 mmHg or higher on repeat measurements 15 minutes apart. Women were randomly assigned to receive either nifedipine or labetalol. Nifedipine 10 mg was give orally with repeated doses of 20 mg every 20 minutes up to a maximum of five doses. Labetalol was given intravenously (20 mg) followed by escalating doses of 40 mg then 80 mg up to a maximum of five doses. The study showed no statistically significant differences in side effects, Apgar score less than 7 at 5 minutes or umbilical artery pH less than 7.0 between the two groups.

Labetalol versus methyldopa

The Cochrane review[174] [EL = 1++] included one RCT ($n = 74$) that compared labetalol with methyldopa. No statistically significant differences were found.

* The authors reported that the dosage was 0.15 g/kg per minute over 6 hours, but this appears to be a typographical error and the results should therefore be treated with caution.

Labetalol versus diazoxide

The Cochrane review[174] [EL = 1++] included one RCT ($n = 90$) that compared labetalol with diazoxide. Women treated with labetalol were statistically significantly less likely to have maternal hypotension than those treated with diazoxide (one RCT, $n = 90$: RR 0.06; 95% CI 0.00 to 0.99). No other statistically significant differences were found.

Nitrates versus magnesium sulphate

The Cochrane review[174] [EL = 1++] included one RCT ($n = 36$) that compared nitrates with magnesium sulphate. No statistically significant differences were found.

Nifedipine versus chlorpromazine

The Cochrane review[174] [EL = 1++] included one RCT ($n = 60$) that compared nifedipine with chlorpromazine. No statistically significant differences were found.

Nifedipine versus prazosin

The Cochrane review[174] [EL = 1++] included one RCT ($n = 130$) that compared nifedipine with prazosin. No statistically significant differences were found.

Nimodipine versus magnesium sulphate

The Cochrane review[174] [EL = 1++] included two RCTs ($n = 1683$) that compared nimodipine with magnesium sulphate. Women treated with nimodipine were statistically significantly less likely to develop persistent high blood pressure than those treated with magnesium sulphate (one RCT, $n = 1650$: RR 0.84; 95% CI 0.76 to 0.93). For specific side effects, women treated with nimodipine were statistically significantly less likely to report 'flushing' than those treated with magnesium sulphate (one RCT, $n = 1650$: RR 0.22; 95% CI 0.12 to 0.40). No other statistically significant differences were found.

Diazoxide versus hydralazine

An RCT[180] [EL = 1+] from Australia compared diazoxide with hydralazine ($n = 97$, 50 versus 47). Women requiring intravenous antihypertensive treatment (97 antenatal period, 27 postnatal period) were randomised to receive either diazoxide (15 mg boluses every 3 minutes until pressure was controlled or 300 mg was given) or hydralazine (5 mg boluses every 20 minutes for up to three doses). Four women in each group were prescribed two oral medications before and after the administration of intravenous medications. The authors reported 24 drug administration protocol violations. The study showed no statistically significant differences between the two groups.

Nitroglycerine versus nifedipine

A double-blind RCT[181] [EL = 1+] from Mexico compared nitroglycerine with nifedipine ($n = 32$, 16 each arm). Women at 24 weeks of gestation or later with uncomplicated severe pre-eclampsia and with no history of chronic hypertension, use of antihypertensive therapy or life-threatening fetal heart-rate changes were eligible to enter the trial. Thirty-two eligible women were randomly allocated to receive either nitroglycerine infusion (5 micrograms/minute) with increases in dose of 5 micrograms/minute every 5 minutes or nifedipine capsules (10 mg) every 30 minutes. Both groups received a loading dose of magnesium sulphate 4 g/250 ml dextrose 5% in water (D5W) intravenously, followed by an intravenous infusion of 1 g/hour for up to 8 hours postpartum. The study showed no statistically significant differences in side effects, caesarean section, post-delivery bleeding above 1000 ml or Apgar score less than 7 at 1 minute and 5 minutes between the two groups.

Table 10.2 Source and level of evidence for comparisons between the various antihypertensive agents

	Hydralazine	Labetalol	Ca blockers	Ketanserin	Urapidil	Epoprostenol	Diazoxide	Methyldopa	Nitrates	Chlorpromazine
Hydralazine	N/A	C [EL = 1++] M [EL = 1++] I [EL = 1+]	C [EL = 1++] M [EL = 1++] I (two) [EL = 1–]	C [EL = 1++] M [EL = 1++]	C [EL = 1++] M [EL = 1++]	C [EL = 1++] M [EL = 1++]	I [EL = 1+]	–	–	–
Labetalol	C [EL = 1++] M [EL = 1++] I [EL = 1+]	N/A	C [EL = 1++] I [EL = 1+]	–	–	–	C [EL = 1++]	C [EL = 1++]	–	–
Ca blockers	C [EL = 1++] M [EL = 1++] I (two) [EL = 1–]	C [EL = 1++] I [EL = 1+	N/A	–	–	–	–	–	I [EL = 1+]	C [EL = 1++]
Magnesium sulphate	–	–	C [EL = 1++]	–	–	–	–	–	C [EL = 1++]	–

C = Cochrane systematic review; I = individual RCT; M = meta-analysis

Table 10.3 Evidence from the Cochrane review, meta-analysis and individual trials for labetalol versus hydralazine (reported as RRs with 95% CIs)

Study	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU	Other
Cochrane[174] [EL = 1++]	3 RCTs, *n* = 69	1 RCT, *n* = 20: no cases	1 RCT, *n* = 20: RR 3.00 (0.79–11.44)	2 RCTs, *n* = 50: no cases	2 RCTs, *n* = 50: RR 0.52 (0.24–1.11)	3 RCTs, *n* = 69: RR 0.71 (0.40–1.24)	–	–	–	3 RCTs, *n* = 69: RR 0.84 (0.01–54.78)	3 RCTs, *n* = 69: RR 0.50 (0.05–4.94)	1 RCT, *n* = 19: RR 0.69 (0.15–3.12)	At 5 minutes: 1 RCT, *n* = 19: RR 0.10 (0.01–1.81)	–	Neonatal hypoglycaemia: 2 RCTs, *n* = 39: RR 1.14 (0.19–6.94)
Magee *et al.*[175] [EL = 1++]	5 RCTs, *n* = 156	–	4 RCTs, *n* = 126: RR 3.4 (1.0–12.5)	4 RCTs, *n* = 122: RR 0.2 (0.0–0.9)	5 RCTs, *n* = 156: RR 0.3 (0.2–0.6)	–	–	–	–	–	Stillbirth: 5 RCTs, *n* = 109: RD = −0.05 (–0.17 to +0.08)	–	–	–	–
Vigil-De Gracia *et al.*[176] [EL = 1+] Panama	Individual RCT, *n* = 200	100 vs 100: no cases	5/100 vs 5/100: RR 1.00 (0.30–3.35)	0/100 vs 2/100: NS	18/100 vs 10/100: RR 1.80 (0.87–3.70)	56/100 vs 51/100: RR 1.10 (0.85–1.42)	1/100 vs 2/100: NS	1/100 vs 0/100: NS	HELLP syndrome: 2/100 vs 2/100: RR 1.0 (0.14–6.96)	6/103 vs 8/102: RR 0.74 (0.27–2.06)	2/103 vs 2/102: NS	26/103 vs 23/102: RR 1.12 (0.69–1.83)	At 1 minute: 20/103 vs 14/102: RR 1.41 (0.76–2.64) At 5 minutes: 4/103 vs 2/102: RR 1.98 (0.37–10.57)	32/103 vs 32/102: RR 0.99 (0.66–1.49)	Neonatal complications: 29/103 vs 27/102: RR 1.06 (0.68–1.66)

NICU = neonatal intensive care unit; RD = respiratory distress

Table 10.4 Evidence from the Cochrane review, meta-analysis and individual trials for calcium-channel blockers versus hydralazine (reported as RRs with 95% CIs)

Study	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU
Cochrane [174] [EL = 1++]	6 RCTs, *n* = 313	–	5 RCTs, *n* = 263: RR 0.33 (0.15–0.70)	3 RCTs, *n* = 199: RR 2.83 (0.12–64.89)	4 RCTs, *n* = 236: RR 0.79 (0.50–1.24)[a]	1 RCT, *n* = 37: RR 0.85 (0.56–1.29)		–	–	3 RCTs, *n* = 203: RR 0.40 (0.09–1.83)	4 RCTs, *n* = 161: RR 1.36 (0.42–4.41)	–	–	–
Magee *et al.*[175] [EL = 1++]	9 RCTs, *n* = 619	–	5 RCTs, *n* = 350: RR 0.7 (0.5–1.1)	6 RCTs, *n* = 485: RR 0.4 (0.1–2.0)	4 RCTs, *n* = 245: RR 1.1 (0.8–1.5)	–	–	–	–	6 RCTs, *n* = 360: RR 0.2 (0.1–0.6)	Stillbirth: 6 RCTs, *n* = 388: RD = −0.01 (−0.03 to +0.02)	–	–	–
Kwawukume *et al.*[177] [EL = 1−] nifedipine Ghana	Individual RCT, *n* = 79	–	5/49 versus 14/35: RR 0.28 (0.11–0.71)	–	–	22/44 versus 24/35: RR 0.73 (0.50–1.06)	–	–	–	–	0/44 versus 2/35: NS	0/44 versus 1/35: NS	–	11/44 versus 13/35: RR 0.67 (0.34–1.31)
Fletcher *et al.*[178] [EL = 1−] isradipine Jamaica	Individual RCT, *n* = 39	–	–	–	–	3/20 versus 2/19: RR 1.43 (0.27–7.61)	–	–	–	–	–	–	–	–

NICU = neonatal intensive care unit; RD = respiratory distress

[a] Specific side effects:
- palpitations: two RCTs, *n* = 87: RR 0.63; 95% CI 0.29 to 1.39
- nausea and/or vomiting: three RCTs, *n* = 120: RR 3.48; 95% CI 1.01 to 11.99
- headache: four RCTs, *n* = 246: RR 1.09; 95% CI 0.50 to 2.36
- flushing: three RCTs, *n* = 120: RR 2.26; 95% CI 0.83 to 6.13
- dyspnoea: one RCT, *n* = 37: RR 0.85; 95% CI 0.06 to 12.59

Table 10.5 Evidence from the Cochrane review, meta-analysis and individual trials for ketanserin versus hydralazine (reported as RRs with 95% CIs)

Study	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU
Cochrane[174] [EL = 1++]	4 RCTs, *n* = 200	2 RCTs, *n* = 64: RR 0.60 (0.08–4.24)	3 RCTs, *n* = 180: RR 4.79 (1.95–11.73)	2 RCTs, *n* = 76: RR 0.26 (0.07–1.03)	3 RCTs, *n* = 120: RR 0.32 (0.19–0.53)	3 RCTs, *n* = 120: RR 0.53 (0.14–2.06)	2 RCTs, *n* = 64: RR 0.14 (0.02–1.10)	1 RCT, *n* = 44: RR 0.11 (0.01–1.95)	Maternal death: 2 RCTs, *n* = 124: RR 0.32 (0.03–2.96 Severe morbidity: 1 RCT, *n* = 56: RR 0.32 (0.09–1.12) HELLP syndrome: 1 RCT, *n* = 44: RR 0.20 (0.05–0.81)	–	2 RCTs, *n* = 116: RR 0.27 (0.05–1.64)	–	–	–
Magee *et al.*[175] [EL = 1++]	4 RCTs, *n* = 190	–	3 RCTs, *n* = 180: RR 1.3 (0.7–2.6)	2 RCTs, *n* = 47: RR 0.4 (0.1–1.4)	2 RCTs, *n* = 64: RR 0.4 (0.2–0.7)	–	–	–	–	2 RCTs, *n* = 100: RR 0.4 (0.1–1.8)	Stillbirth: 3 RCTs, *n* = 144: RD = −0.04 (−0.11 to +0.03)	–	–	–

HELLP = haemolysis, elevated liver enzymes and low platelet count; NICU = neonatal intensive care unit; RD = respiratory distress

Table 10.6 Evidence from the Cochrane review, meta-analysis and individual trials for urapidil versus hydralazine (reported as RRs with 95% CIs)

Study	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU
Cochrane[174] [EL = 1++]	2 RCTs, *n* = 59	1 RCT, *n* = 26: no cases	2 RCTs, *n* = 59: RR 1.38 (0.06–31.14)	1 RCT, *n* = 33: RR 0.22 (0.02–2.13)	2 RCTs, *n* = 59: RR 0.59 (0.10–3.58)	2 RCTs, *n* = 59: RR 0.77 (0.51–1.16)	1 RCT, *n* = 33: RR 0.15 (0.01–3.46)	–	–	–	Stillbirth: 1 RCT, *n* = 26: no cases Neonatal death: 2 RCTs, *n* = 59: RR 0.66 (0.08–5.25)	–	–	–
Magee *et al.*[175] [EL = 1++]	2 RCTs, *n* = 59	–	2 RCTs, *n* = 26 no cases	1 RCTs, *n* = 33: RR 0.2 (0.0–2.1)	1 RCT, *n* = 29: RR 1.4 (0.2–11.1)	–	–	–	–	2 RCTs, *n* = 55; RR 0.1 (0.0–1.8)	Stillbirth: 2 RCTs, *n* = 56: no cases	–	–	–

NICU = neonatal intensive care unit

Table 10.7 Evidence from the Cochrane review, meta-analysis and individual trials for epoprostenol versus hydralazine (reported as RRs with 95% CIs)

Study	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU	Others
Cochrane[174] [EL = 1++]	1 RCT, *n* = 47	–	1 RCT, *n* = 47: RR 0.23, (0.01–4.47)	–	1 RCT, *n* = 47: RR 1.14 (0.08–17.11)	1 RCT, *n* = 47: RR 0.74 (0.50–1.10)	–	–	–	–	1 RCT, *n* = 47: RR 1.14 (0.08–17.11)	–	–	–	Ventilation: 1 RCT, *n* = 47: RR 0.32 (0.08–1.80)
Magee *et al.*[175] [EL = 1++]	1 RCT, *n* = 47	–	1 RCT, *n* = 50: RR 0.2 (0.0–4.5)	–	–	–	–	–	–	1 RCT, *n* = 47: RR 0.9 (0.5–1.5)	Stillbirth: 1 RCT, *n* = 47: no cases	–	–	–	–

NICU = neonatal intensive care unit

Table 10.8 Evidence from the Cochrane review, meta-analysis and individual trials for labetalol versus calcium-channel blockers (reported as RRs with 95% CIs)

Study	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU	Others
Cochrane[174] nicardipine	1 RCT, *n* = 60	1 RCT ,*n* = 60: RR 1.22 (0.59–2.51)	–	1 RCT, *n* = 60: no cases	Specific side effects[a]	–	–	–	–	–	–	–	–	–	–
Vermillion *et al.*[179] nifedipine USA	Individual RCT, *n* = 50 [EL = 1+]	–	–	–	Specific side effects[b]	–	–	–	–	–	–	–	At 5 minutes: 2/14 vs 1/15: NS	–	Umbilical artery pH < 7.0: 1/15 vs 1/14: RR 1.07 (0.07–15.54)

NICU = neonatal intensive care unit

[a] Specific side effects:
- nausea and/or vomiting: 1 RCT, *n* = 60: RR 1.00; 95% CI 0.07 to 15.26
- palpitation: 1 RCT, *n* = 60: RR 0.14; 95% CI 0.01 to 2.65

[b] Specific side effects (for women randomised before/after delivery):
- headache: 5/25 versus 4/25: NS
- flushing: 2/25 versus 2/25: NS
- nausea: 2/25 versus 2/25: NS

Table 10.9 Evidence from the Cochrane review[174] for comparisons between various antihypertensives (reported as RRs with 95% CIs)

Comparison	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU	Others
Labetalol versus methyldopa	1 RCT, *n* = 74	–	1 RCT, *n* = 72: RR 1.19 (0.74–1.94)	–	–	1 RCT, *n* = 72: RR 0.85 (0.56–1.30)	–	–	–	–	1 RCT, *n* = 72: RR 4.49 (0.22–90.33)	–	–	1 RCT, *n* = 72: RR 1.06 (0.66–1.71)	Small for gestational age: 1 RCT, *n* = 72: RR 0.78 (0.43–1.39)
Labetalol versus diazoxide	1 RCT, *n* = 90	–	1 RCT, *n* = 90: RR 0.50 (0.13–1.88)	1 RCT, *n* = 90: RR 0.06 (0.00–0.99)	–	1 RCT, *n* = 90: RR 0.43 (0.18–1.02)	–	–	–	–	1 RCT, *n* = 90: RR 0.14 (0.01–2.69)	–	–	–	–
Nitrates versus magnesium sulphate	1 RCT, *n* = 36	1 RCT, *n* = 36: no cases	1 RCT, *n* = 36: RR 0.14, (0.01–2.58)	–	–	1 RCT, *n* = 36: RR 0.19 (0.07–0.53)	–	–	–	–	–	–	–	–	–
Nifedipine versus chlorpromazine	1 RCT, *n* = 60	1 RCT, *n* = 55: RR 2.52 (0.11–59.18)	1 RCT, *n* = 60: RR 0.09 (0.01–1.57)	–	–	1 RCT, *n* = 55: RR 0.80 (0.60–1.05)	1 RCT, *n* = 60: RR 0.76 (0.27–2.18)	–	CVA: 1 RCT, *n* = 60: no cases.	–	–	–	–	–	Baby intubated at delivery: 1 RCT, *n* = 60: RR 0.73 (0.49–1.09)
Nifedipine versus prazosin	1 RCT, *n* = 130	1 RCT, *n* = 145: no cases	–	–	–	1 RCT, *n* = 145: RR 0.90 (0.72–1.13	1 RCT, *n* = 145: RR 0.96 (0.40–2.28)	1 RCT, *n* = 145: RR 0.19 (0.02–1.60)	HELLP syndrome; 1 RCT, *n* = 145: RR 0.48 (0.04–5.17) Kidney failure: 1 RCT, *n* = 145: RR 0.48 (0.04–5.17)	–	1 RCT, *n* = 149: RR 0.46 (0.18–1.13)	1 RCT, *n* = 130: RR 1.22 (0.52–2.82)	–	1 RCT, *n* = 130: RR 0.78 (0.49–1.23)	–
Nimodipine versus magnesium sulphate	2 RCTs, *n* = 1683	2 RCTs, *n* = 1683: RR 2.24 (1.06–4.73)	1 RCT, *n* = 1650: RR 0.84 (0.76–0.93)	1 RCT, *n* = 1650: RR 0.72, (0.23–2.27)	Specific side effects[a]	2 RCTs, *n* = 1683: RR 0.97 (0.89–1.06)	–	–	–	–	–	–	–	–	–

NICU = neonatal intensive care unit

[a] Specific side effects:
- headache: one RCT, *n* = 1650: RR 1.06; 95% CI 0.71 to 1.58
- flushing: one RCT, *n* = 1650: RR 0.22; 95% CI 0.12 to 0.40
- nausea and/or vomiting: one RCT, *n* = 1650: RR 0.86; 95% CI 0.59 to 1.24

Table 10.10 Evidence from individual RCTs for comparisons between various antihypertensives (reported as RRs with 95% CIs)

Comparison and study	Total number of RCTs and participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary oedema	Other maternal outcomes	Fetal heart rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Apgar < 7	Admission to NICU	Others
Diazoxide versus hydralazine Hennessy *et al.*[180] Australia	Individual RCT, *n* = 97 [EL = 1+]	–	–	–	–	38/50 versus 33/47: RR 1.08 (0.85–1.38)	–	–	–	Non-reassuring CTG required delivery: 13/52 versus 12/49: RR 1.02 (0.52–2.02)	1/52 versus 3/49: RR 0.31 (0.03–2.92)	14/52 versus 13/49: RR 1.01 (0.53–1.94)	At 5 minutes: 4/52 versus 4/49: RR 0.94 (0.25–3.56)	–	Neonatal hypoglycaemia: 6/52 versus 5/49: RR 1.13 (0.37–3.47)
Nitroglycerine versus nifedipine Manzur-Verastegui *et al.*[181] Mexico	Individual RCT, *n* = 32 [EL = 1+]	–	–	–	Specific side effects[a]	11/16 versus 12/16: RR 0.92 (0.59–1.42)	–	–	Post-delivery bleeding > 1000 ml: 1/16 versus 3/16: RR 0.33 (0.04–2.88)	–	16 versus 16: no cases	–	At 1 minute: 2/16 versus 7/16: NS At 5 minutes: 1/16 versus 0/16: NS	–	–

CTG = cardiotocography; NICU = neonatal intensive care unit

[a] Specific side effects:
- flushing: 4/16 versus 6/16: NS
- headache: 3/16 versus 2/16: NS
- palpitations: 3/16 versus 2/16: NS
- nausea: 0/16 versus 1/16: NS

Evidence statement

A Cochrane systematic review and a published meta-analysis considered the effectiveness of antihypertensives for treatment of severe hypertension. [EL = 1++] Both were based on a large number of studies, although the emphasis of the analyses differed between the two; the Cochrane systematic review compared pairs of antihypertensive agents, whereas the meta-analysis focused specifically on comparisons between hydralazine and other antihypertensive agents.

Labetalol versus hydralazine

The Cochrane review [EL = 1++] showed no statistically significant differences between the two drugs in the primary and secondary outcomes set by the GDG.

The meta-analysis [EL = 1++] showed that women treated with labetalol were statistically significantly more likely to develop persistent high blood pressure than those treated with hydralazine. However, they were less likely to have maternal hypotension and suffer from side effects.

The individual RCT [EL = 1+] showed no differences between the two drugs in primary and secondary outcomes.

Calcium-channel blockers versus hydralazine

Both the Cochrane review [EL = 1++] and an individual extra RCT [EL = 1−] showed that women treated with calcium-channel blockers were statistically significantly less likely to develop persistent high blood pressure than those treated with hydralazine.

The meta-analysis [EL = 1++] showed that babies of women treated with calcium-channel blockers were statistically significantly less likely to have fetal heart decelerations than those treated with hydralazine. No other statistically significant results were found.

Ketanserin versus hydralazine

The Cochrane review [EL = 1++] showed that women treated with ketanserin were statistically significantly more likely to develop persistent high blood pressure but were less likely to have side effects or develop HELLP syndrome than those treated with hydralazine.

The meta-analysis [EL = 1++] showed that women treated with ketanserin were statistically significantly less likely to have side effects. No other results were statistically significantly different between the two groups.

Urapidil versus hydralazine

Both the Cochrane review [EL = 1++] and the meta-analysis [EL = 1++] showed no statistically significant differences between the two groups in the primary and secondary outcomes.

Epoprostenol versus hydralazine

Both the Cochrane review [EL = 1++] and the meta-analysis [EL = 1++] showed no statistically significant differences between the two groups in the primary and secondary outcomes.

Labetalol versus calcium-channel blockers

Both the Cochrane review and an extra individual RCT [EL = 1+] showed no statistically significant differences between the two groups in the primary and secondary outcomes.

Labetalol versus diazoxide

The Cochrane review showed that women treated with labetalol were statistically significantly less likely to develop hypotension than those treated with methyldopa. No other statistically significant differences were found.

Labetalol versus methyldopa

The Cochrane review showed no statistically significant differences between the two groups in the primary and secondary outcomes.

Nitrates versus magnesium sulphate

The Cochrane review showed no statistically significant differences between the two groups in the primary and secondary outcomes.

Nifedipine versus chlorpromazine

The Cochrane review showed no statistically significant differences between the two groups in the primary and secondary outcomes.

Nifedipine versus prazosin

The Cochrane review showed no statistically significant differences between the two groups in the primary and secondary outcomes.

Nimodipine versus magnesium sulphate

The Cochrane review showed that women treated with nimodipine were statistically significantly less likely to develop persistent high blood pressure than those treated with magnesium sulphate. They were also less likely to suffer from 'flushing' as a side effect. No other statistically significant differences were found.

Diazoxide versus hydralazine

Individual RCT [EL = 1+] showed no statistically significant difference in primary and secondary outcomes between the two groups.

Nitroglycerine versus nifedipine

Individual RCT [EL = 1+] showed no statistically significant difference in primary and secondary outcomes between the two groups.

GDG interpretation of the evidence

There are no placebo controlled trials of antihypertensive treatment in women with severe pre-eclampsia in a critical care setting to inform the GDG but the consensus was that lowering blood pressure in women with severe hypertension is necessary. There did not appear to be any evidence that one particular antihypertensive agent was preferable in lowering blood pressure or in adverse outcomes for the mother or the fetus.

The GDG have recommended the commonly used antihypertensive regimens. There is no clear advantage in the route of delivery of antihypertensive therapy in the trials but the GDG agreed that route of administration could be oral or intravenous for labetalol, oral for nifedipine and intravenous for hydralazine.

Labetalol is the only drug licensed for the treatment of hypertension in pregnancy.

The side effect profile for these drugs was similar with no drug showing a clear advantage in minimising side effects. However, there is some advantage of labetalol over hydralazine for all maternal side effects, but the overall numbers in the studies was small.

Preloading or co-administration using no more than 500 ml of intravenous crystalloid fluid reduces the risk of sudden severe hypotension seen with intravenous hydralazine and may be considered prior to birth. Although there are few data on pulmonary oedema in the trials the main indication for the prevention of sudden hypotension is protection of the fetal circulation. There is less justification for fluid loading following birth.

Overall the cost of treatment was considered by the GDG. Although there is little difference between the costs of different antihypertensives, oral administration is likely to be cheaper than intravenous administration. The GDG noted that the mode of administration would depend on the condition of the woman, but where feasible oral administration should be preferred to intravenous administration because it is likely to be cost effective.

The evidence is not available to support a specific target blood pressure, nor the time to achieve that blood pressure. The GDG consensus was to avoid a rapid and precipitate fall in the maternal blood pressure and to closely observe the woman for side effects and response to treatment. The GDG considered a fall in blood pressure to 150/80–100 mmHg appropriate with maintenance of the blood pressure at this level to avoid placental underperfusion.

Recommendations

Treat women with severe hypertension who are in critical care during pregnancy or after birth immediately with one of the following:

- labetalol† (oral or intravenous)
- hydralazine (intravenous)
- nifedipine† (oral).

In women with severe hypertension who are in critical care, monitor their response to treatment:

- to ensure that their blood pressure falls
- to identify adverse effects for both the woman and the fetus
- to modify treatment according to response.

Consider using up to 500 ml crystalloid fluid before or at the same time as the first dose of intravenous hydralazine in the antenatal period.

In women with severe hypertension who are in critical care, aim to keep systolic blood pressure below 150 mmHg and diastolic blood pressure between 80 and 100 mmHg.

Research recommendation

What is the most clinically effective antihypertensive agent for severe pre-eclampsia in a critical care setting?

Why this is important

The choice of antihypertensive treatment in severe hypertension in the critical care setting has evolved historically rather than scientifically and there are few useful comparisons. Dosage and route of administration vary, as does use of different routes or doses from those shown to be effective in trials.

Effective and safe control of severe hypertension is the most important aspect of critical care management, as the main cause of maternal death is the consequence of poorly controlled hypertension. Randomised controlled trials should evaluate antihypertensive treatments (labetalol, nifedipine and hydralazine) for women with severe hypertension in pregnancy in the critical care setting. Comparisons should be made between the different antihypertensives, with assessment against outcomes such as persistence of severe hypertension after completion of therapy or by the need for additional treatment, maternal side effects and the effect on the fetus and baby.

10.4 Corticosteroids for fetal lung maturation

Clinical effectiveness

A Cochrane systematic review investigated the effect of antenatal corticosteroids for accelerating fetal lung maturation in women at risk of preterm birth.[182] [EL = 1++] A subgroup analysis of the review presented data for women with hypertensive syndromes in pregnancy. The review assessed all RCTs comparing antenatal corticosteroid administration (betamethasone, dexamethasone or hydrocortisone) with placebo or no treatment given to women before anticipated preterm birth. Quasi-randomised trials were excluded. Trials that tested the effect of corticosteroid along with other co-interventions were also excluded.

Five RCTs were included in the 'women with hypertension syndromes in pregnancy' subgroup analysis. One trial ($n = 220$) included only women with severe pre-eclampsia. The other trials included all women with preterm birth but with results for those with hypertension in

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

pregnancy syndromes reported separately. Methods of randomisation were properly described in two of these trials but not stated in the other three.

Babies from pregnancies complicated by hypertension syndromes treated with corticosteroids had a statistically significantly reduced risk of neonatal death (two RCTs, $n = 278$ babies; RR 0.50; 95% CI 0.29 to 0.87), respiratory distress syndrome (five RCTs, $n = 382$ babies; RR 0.50; 95% CI 0.35 to 0.72) and cerebroventricular haemorrhage (two RCTs, $n = 278$ babies; RR 0.38; 95% CI 0.17 to 0.87). They were also statistically significantly less likely to need mechanical ventilation (one RCT, $n = 200$ babies: RR 0.62; 95% CI 0.41 to 0.91) or to have systemic infection in the first 48 hours of life (one RCT, $n = 200$ babies: RR 0.46; 95% CI 0.26 to 0.84). In pregnancies complicated by hypertension syndromes, no statistically significant differences between groups treated with antenatal corticosteroids and controls were reported for combined fetal and neonatal death, fetal death, birthweight, chorioamnionitis or puerperal sepsis. The Cochrane review did not report any direct comparisons between different types of corticosteroids (betamethasone, dexamethasone and hydrocortisone).

A large non-randomised retrospective study has suggested that babies exposed to betamethasone antenatally have less neonatal cystic periventricular leucomalacia than those exposed to antenatal dexamethasone.[183] [EL = 2 –] Another historical cohort study reported a statistically significant reduction in the number of neonatal deaths with the use of dexamethasone compared with betamethasone (OR 1.66; 95% CI 1.07 to 2.57; $P < 0.05$).[184] [EL = 2 –]

Evidence statement

A Cochrane review [EL = 1++] showed that antenatal corticosteroids in women with hypertensive syndromes statistically significantly reduced the risk of neonatal death, respiratory distress syndrome and cerebroventricular haemorrhage. Babies of women treated with corticosteroids were also less likely to need mechanical ventilation or have infections in the first 48 hours of life.

Two retrospective studies [EL = 2 –] showed that betamethasone was associated with fewer neonatal adverse effects (neonatal deaths or cystic periventricular leucomalacia) than dexamethasone.

GDG interpretation of the evidence

There is good evidence to suggest that the use of steroids antenatally in pregnancies complicated by hypertensive disorders will enhance fetal lung maturity and reduce the incidence of the complications of preterm birth, especially respiratory distress syndrome, when the pregnancy is at less than 34 weeks. The evidence is less clear when the pregnancy is between 34 and 37 weeks, but the GDG considers that there is likely to be benefit in this group of women. The preferred steroid is two doses of betamethasone 12 mg administered intramuscularly 24 hours apart, with betamethasone being preferred over dexamethasone because it is associated with fewer neonatal adverse effects (neonatal death and cystic periventricular leucomalacia); the two drugs are similarly priced and so the recommendation to use betamethasone is likely to be cost effective.

In formulating the recommendations, the GDG noted the results of the Antenatal Steroid for Term Elective Caesarean Section (ASTECS) study, which showed that babies born after 37 weeks by elective caesarean section also benefit from antenatal corticosteroid administration.[185]

Recommendation

If birth is considered likely within 7 days in women with pre-eclampsia:

- give two doses of betamethasone * 12 mg intramuscularly 24 hours apart in women between 24 and 34 weeks
- consider giving two doses of betamethasone* 12 mg intramuscularly 24 hours apart in women between 35 and 36 weeks.

* In this guideline, drug names are marked with an asterisk if they do not have UK marketing authorisation for the indication in question at the time of publication (August 2010). Informed consent should be obtained and documented.

10.5 Corticosteroids to manage HELLP syndrome

Clinical effectiveness

Corticosteroids have been used in women (antepartum and postpartum) diagnosed with HELLP syndrome. One Cochrane systematic review[186] [EL = 1++] studied two comparisons: dexamethasone plus standard treatment versus standard treatment alone, and dexamethasone versus betamethasone. One additional RCT[187] [EL = 1+] compared dexamethasone with placebo while another RCT[188] [EL = 1+] compared dexamethasone with betamethasone.

Dexamethasone plus standard treatment versus standard treatment alone

A Cochrane review investigated the effects of corticosteroids in women with HELLP syndrome (diagnosed clinically and by biochemical parameters) during pregnancy or shortly after delivery.[186] [EL = 1+] All RCTs and trials that used pseudo-randomised methods, such as alternate allocation, were included. Five studies were included, three of which employed adequate randomisation and allocation concealment methods. However, blinding was not described in any. There was significant loss to follow-up in one study. Only 25 out of the original 40 participants randomised were accounted for in the results section. Intention to treat analysis was not performed in this study. The other studies had no loss to follow-up.

No statistically significant differences were found in maternal death or neonatal deaths. No cases of maternal morbidity were reported in either group (liver haematoma or rupture, pulmonary oedema, kidney failure or placental abruption). There were no statistically significant differences in the likelihood of having perinatal intraventricular haemorrhage, respiratory distress syndrome or retrolental fibroplasias. No intracerebral haemorrhagic events or necrotising enterocolitis were recorded.

In secondary outcomes, no statistically significant differences were found in postpartum sepsis, caesarean section or increase in platelet count over 48 hours. However, there were statistically significant differences in the mean number of hospital stay days post-randomisation (one RCT, $n = 30$: WMD −4.50 days; 95% CI −7.13 to −1.87 days) and time interval from randomisation to delivery (one RCT, $n = 25$: WMD 26.00 hours; 95% CI 17.17 to 34.83 hours), both of which were in favour of women allocated to dexamethasone treatment.

A Colombian double-blind RCT compared the efficacy of dexamethasone with placebo for the treatment of women (pregnant or puerperal) who developed hypertension during pregnancy and met the criteria for HELLP syndrome classes 1 and 2.[187] [EL = 1+] One hundred and thirty-two women were randomised to receive either dexamethasone ($n = 66$) or placebo ($n = 66$). The baseline characteristics of women in the two groups were comparable. Randomisation was done by the use of stratified and random permuted blocks of four, and concealment of allocation was ensured by using opaque envelopes. Dexamethasone 10 mg was given intravenously every 12 hours until delivery and three further times after delivery. Women in the placebo group were given sterile water at a similar schedule.

There was no statistically significant difference in maternal mortality between the two groups (three of 66 versus one of 66: RR 3.0; 95% CI 0.32 to 28.1). There were also no statistically significant differences between the two groups in the maternal complications of acute kidney failure, oliguria, pulmonary oedema, eclampsia, infections or the need for platelets or plasma transfusion. The mean duration of hospitalisation of women was not statistically significantly different between the two groups. No statistically significant differences were found in the time to recovery of platelet counts (hazard ratio 1.2; 95% CI 0.8 to 1.8), LDH (hazard ratio 0.9; 95% CI 0.5 to 1.50) or AST (hazard ratio 0.6; 95% CI 0.4 to 1.1).

The results related to both pregnant and puerperal groups. Stratified analysis showed no differences in the occurrence of complications, recovery of laboratory parameters, transfusion need or duration of hospitalisation.

Dexamethasone versus betamethasone

There was only one study from the Cochrane review described above[186] [EL = 1+] that compared dexamethasone with betamethasone ($n = 40$). No maternal death occurred. Perinatal mortality was not statistically significantly different between the two groups (RR 0.95; 95% CI

0.15 to 6.08). There were no cases of liver haematoma or rupture, pulmonary oedema or placental abruption in either group. There was a statistically significant difference in maternal oliguria (RR 0.06; 95% CI 0.00 to 0.93) in favour of women randomised to dexamethasone. No statistically significant differences were found in neonates' need for ventilatory support or having respiratory distress syndrome. No cases of intracerebral haemorrhage or necrotising enterocolitis were recorded.

There were statistically significant differences in favour of women allocated to dexamethasone in the adjusted time-average change from baseline in the following secondary outcomes: the mean arterial pressure decrease (WMD −7.50 mmHg; 95% CI −8.37 to −6.63 mmHg), the mean increase in urinary output (WMD 24.80 ml/day; 95% CI 19.58 to 30.02 ml/day), the mean increase in platelet count (WMD 8.10 × 10^9/litre; 95% CI 6.23 to 9.97 × 10^9/litre), the mean decrease in LDH activity (WMD −4.20 U/litre; 95% CI −88.22 to −20.18 U/litre) and the mean decrease in AST activity (U/L) (WMD −30.30 U/litre; 95% CI −36.06 to −24.54 U/litre).

The number of women needing acute antihypertensive therapy in the dexamethasone group differed statistically significantly compared with those allocated to betamethasone (RR 0.29; 95% CI 0.12 to 0.73).

There were no statistically significant differences between the two groups with regard to the number of neonates with a Apgar score less than 7 at 5 minutes, neonatal sepsis, neonatal hyperbilirubinaemia or mean time to discharge.

An RCT in the USA compared the efficacy of dexamethasone with betamethasone for the treatment of women with HELLP syndrome first manifesting itself in the postpartum period.[188] [EL = 1+] Women who developed HELLP syndrome or any other manifestation of pre-eclampsia in the antepartum period were excluded. Thirty-six women were randomised to receive either dexamethasone 10 mg intravenously every 12 hours ($n = 18$) or betamethasone 12 mg intramuscularly every 24 hours ($n = 18$). The baseline characteristics of women in the two groups were comparable except for LDH level, which was statistically significantly higher in the dexamethasone group (1831.7 ± 1140.6 U/litre versus 1193.6 ± 496.4 U/litre; $P < 0.05$). Randomisation was by sequentially numbered sealed opaque envelopes constructed from a random number table.

The time to discharge from the obstetric recovery room was not statistically significant between groups. Reduction in mean arterial blood pressure was more pronounced in the dexamethasone group compared with the betamethasone group (−15.3 ± 1.4 mmHg versus −7.5 ± 1.4 mmHg; $P < 0.01$). Women in the dexamethasone group required statistically significantly less antihypertensive treatment than the betamethasone group (one of 18 versus nine of 18: RR 0.11; 95% CI 0.02 to 0.79) and also had a decreased need for readmission to the obstetric recovery room (none of 18 versus four of 18: RR 0.11; 95% CI 0.006 to 1.924).

Evidence statement

In women with HELLP syndrome during pregnancy or shortly after delivery, a Cochrane review [EL = 1++] showed that the use of corticosteroids was no different from placebo in terms of maternal or neonatal complications. However, women who were allocated to corticosteroids stayed in hospital for statistically significantly shorter periods and had statistically significantly shorter time intervals between randomisation and delivery. An RCT [EL = 1+] also showed no difference in maternal or neonatal complications between women treated with corticosteroids and placebo. Hospital duration and time to recovery for platelets, LDH and AST were also similar in both groups. The results were found in both pregnant and puerperal groups.

When comparing dexamethasone with betamethasone use in women with HELLP syndrome (antenatally or postnatally), a Cochrane review [EL = 1+] showed no statistically significant difference in the two groups in terms of maternal or neonatal complications. However, those treated with dexamethasone had statistically significantly higher time-average change in arterial pressure decrease, urinary output increase, platelet count increase, and LDH and AST decrease. They were also statistically significantly less likely to need acute antihypertensive therapy. An RCT [EL = 1+] in women with postpartum HELLP syndrome showed that those treated with dexamethasone were more likely to have reduction in arterial blood pressure than those treated

with betamethasone. They were also less likely to require antihypertensive treatment or to need readmission to the obstetric recovery room.

GDG interpretation of the evidence

There is high-quality evidence that corticosteroids used in the management of HELLP syndrome do not improve any clinically important outcomes either antenatally or postnatally. Two studies into the use of corticosteroids in HELLP syndrome had different conclusions with respect to antenatal and postnatal stays, which may be an important clinical outcome.

Recommendation

Do not use dexamethasone or betamethasone for the treatment of HELLP syndrome.

Research recommendation

Does the use of dexamethasone in HELLP syndrome have clinical utility?

Why this is important

HELLP syndrome is a variant of severe pre-eclampsia where hypertension is less marked but where there is severe involvement of both the liver and the coagulation system. In addition to the usual complications of severe pre-eclampsia there is a risk of liver failure and bleeding.

Studies carried out to determine if steroid injections improve laboratory results have been relatively small and have not clearly shown clinically important benefits. Randomised controlled trials should be carried out in women with HELLP syndrome to assess the clinical utility of dexamethasone compared with placebo control based on outcomes associated with HELLP syndrome (delay to birth; time to hospital discharge following birth; severe maternal complications; serious neonatal complications and long-term outcomes).

10.6 Fluid balance and volume expansion

Clinical effectiveness

An RCT conducted in the Netherlands investigated the use of a volume expansion protocol in women with severe hypertensive disorders of pregnancy (severe pre-eclampsia, HELLP syndrome, and concomitant IUGR) who presented with a viable singleton pregnancy at a gestational age between 24 and 34 weeks.[189] [EL = 1+] Exclusion criteria included severe fetal distress or lethal fetal congenital abnormalities, language difficulties, or if plasma volume expansion had already been given.

Women were randomly allocated by use of computer within two bands of gestational age (between 24^{+0} and 29^{+6} weeks, and between 30^{+0} and 33^{+6} weeks) into either the volume expansion group ($n = 111$) or the no volume expansion group ($n = 105$). The software concealed the group allocation until the woman's details had been entered. Reasons for leaving the study were reported. Baseline characteristics of women in two groups were comparable.

The volume expansion group received 250 ml of 6% hydroxy-ethylstarch (HES) over 4 hours twice a day. Antihypertensives (intravenous ketanserine) were used to achieve diastolic blood pressure of 85–95 mmHg. Additional medication (oral labetalol, methyldopa and nifedipine and occasionally intravenous dihydralazine) was used when necessary. Restricted amounts of sodium chloride 0.9% were infused with medications in between the infusions of HES. Fluid treatment was discontinued if clinical signs of pulmonary oedema were observed.

In the no volume expansion group, antihypertensives (methyldopa) were used to achieve diastolic blood pressure of 95–105 mmHg. Additional medication (oral labetalol, nifedipine and intravenous ketanserine and occasional intravenous dihydralazine) was used when necessary. Restricted amounts of sodium chloride 0.9% were infused with intravenous medication.

Magnesium sulphate was used for preventing and treating eclampsia. One course of intramuscular betamethasone (two doses of 11.4 mg with a 24 hour interval in between) was given when delivery was considered imminent before 32 weeks of gestation.

There was a trend towards a longer pregnancy in the control group (by 10.5 days; 95% CI 0.2 to 440 days) compared with the treatment group (7.4 days; 95% CI 0.1 to 35 days; $P = 0.054$). There was no difference in fetal or postnatal death. Liveborn neonates for women in the volume expansion group were statistically significantly more likely to need ventilation or respiratory support (78 of 98 versus 60 of 98: RR 1.3; 95% CI 1.08 to 1.57). There was no statistically significant difference in major maternal morbidity but there were statistically significantly more caesarean sections in the treatment group (96 of 98 versus 88 of 98: RR 1.10; 95% CI 1.02 to 1.17). Neither neurological scores nor composite neonatal morbidity differed statistically significantly (neonatal morbidities: respiratory distress syndrome, chronic lung disease, intraventricular haemorrhage, progressive ventricular dilation, necrotising enterocolitis, sepsis/meningitis or patent ductus arteriosus). However, episodes of neonatal morbidity were statistically significantly higher in the treatment group (93 of 98 versus 80 of 98: RR 1.26; 95% CI 1.05 to 1.30).

Babies ($n = 172$) born to women in the RCT discussed above were followed up for a year ($n = 82$ treatment, $n = 90$ control).[190] [EL = 1+] The follow-up study assessed the mental and psychomotor development of the babies using the Touwen Scale and the Bayley Scales of Infant Development II that includes two standardised development indices: the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). Adverse neurodevelopmental infant outcome was defined as an MDI/PDI score < 70 and/or an abnormal Touwen score. The mean score was not different between the randomisation groups on any of these scales. There was no difference in the number of cases shown as moderately or severely delayed by the Bayley test and nor was there a difference in the cases shown as suspect or abnormal in the Touwen test.

A Dutch case–control study compared the results of nulliparous women with severe pre-eclampsia who were treated with a volume expansion protocol with those receiving no volume expansion treatment.[191] [EL = 2+] Women with known pre-existing hypertensive, cardiac or kidney disease were excluded. Cases ($n = 57$) and controls ($n = 57$) were recruited from two medical centres in the Netherlands and matched retrospectively according to gestational age at admission (maximum 1 week difference). Characteristics at admission for the two groups were comparable.

The volume expansion group was admitted to ICU for central haemodynamic monitoring. If the pulmonary capillary wedge pressure (PCWP) was less than 10 mmHg and/or the cardiac index was less than 3.5 litres/minute per m², women received intravenous pasteurised plasma (250 ml/hour) to maintain the PCWP at 10–12 mmHg and a cardiac index of 3.5–4.6 litres/minute per m². If the cardiac index remained below 3.5 and the diastolic blood pressure above 100 mmHg, women received intravenous dihydralazine (1 mg/hour), followed by hourly increments of 1 mg. Methyldopa was used when the desired reduction was not obtained. After stabilisation, women were transferred to the ward where plasma volume expansion and antihypertensive treatments were continued: bed rest, continuous monitoring, and diazepam where eclampsia was thought to be imminent or convulsions occurred; diet was unrestricted. Women in the control group had bed rest, no intravenous fluids, and a diet with less than 400 mg sodium per 24 hours. Women with symptoms of headache, upper abdominal pain or visual disturbances received phenobarbital 30 mg orally three times a day. Antihypertensive medication was given when diastolic blood pressure reached and remained above 115 mmHg (intravenous dihydralazine). Intravenous magnesium sulphate was administered as anticonvulsant treatment.

No statistically significant differences were found in prolongation of pregnancy between the two groups. SGA infants (less than 2.3 percentile) were statistically significantly less frequent in the volume expansion group than in the control group (five of 57 versus 19 of 57: OR 0.19; 95% CI 0.07 to 0.56). However, babies born to women in the volume expansion group were statistically significantly more likely to need artificial ventilation (27 of 57 versus eight of 57: OR 5.51; 95% CI 2.22 to 13.70) and to have patent ductus arteriosus (nine of 57 versus two of 57:

OR 5.16; 95% CI 1.06 to 25.04). Other neonatal complications were not statistically significantly different between the two groups. For maternal complications, no statistically significant differences were found for HELLP syndrome, placental abruption, pulmonary oedema, postpartum cardiomyopathy or postpartum renal insufficiency.

Evidence statement

In women with severe hypertension during pregnancy, an RCT [EL = 1+] that compared women who received volume expansion treatment with those who received no volume expansion treatment showed no statistically significant difference in major maternal morbidity, but there were more caesarean sections in the treatment group. On a 1-year follow-up of the babies, no statistically significant differences were found in mental or psychomotor development of babies from the two groups. The use of volume expansion treatment was not statistically significantly different from the no volume expansion protocol in terms of fetal or postnatal death. Neither neurological scores nor composite neonatal morbidity differed statistically significantly between liveborn neonates for women from the two groups. However, episodes of neonatal morbidity were statistically significantly higher in the treatment group. Babies born to women in the treatment group were also statistically significantly more likely to need ventilation or respiratory support.

A case–control study [EL = 2+] showed no statistically significant difference in prolongation of pregnancy between the two groups. For maternal complications, no statistically significant differences were found between the two groups. SGA infants were statistically significantly less frequent in the volume expansion group than in the control group. However, babies born to women in the volume expansion group were statistically significantly more likely to need artificial ventilation and to have patent ductus arteriosus. Other neonatal complications were not statistically significantly different between the two groups.

GDG interpretation of the evidence

The two studies reviewed both suggested that neonatal morbidity may be higher when maternal fluid expansion is used. In one study there was a reduction in the incidence of SGA babies. There were no obvious maternal advantages.

The Confidential Enquiry into Maternal Deaths in the UK reported six deaths in 1994–96 due to adult respiratory distress syndrome (ARDS) that appeared to be related to poor fluid management in women with eclampsia or pre-eclampsia.[192] Recommendations made on the basis of these reported deaths advised that senior medical involvement and care was essential when intravenous fluids were being considered. This advice is thought to have resulted in the fact that by 2003–05 no deaths due solely to fluid mismanagement and ARDS were reported.[192]

The GDG's view is that volume expansion (fluid loading) should be used only if hydralazine (a vasodilator) is the antenatal antihypertensive. Fluid loading in women taking hydralazine will help to reduce severe hypotension.

Recommendations

Do not use volume expansion in women with severe pre-eclampsia unless hydralazine is the antenatal antihypertensive.

In women with severe pre-eclampsia, limit maintenance fluids to 80 ml/hour unless there are other ongoing fluid losses (for example, haemorrhage).

10.7 Caesarean section versus induction of labour

Clinical effectiveness

Caesarean section without labour versus labour induction

A Nigerian RCT compared caesarean section with labour induction in primigravida with singleton cephalic presentation and antenatal or imminent eclampsia and a closed cervical os.[193] [EL = 1–] Fifty women were randomised to have caesarean section ($n = 25$) or labour induction ($n = 25$).

Labour was induced using misoprostol (50 mg) and women were re-evaluated after 4 hours. If the woman went into labour, another 50 mg of misoprostol was inserted and the second stage of labour was shortened by the use of outlet forceps. If labour did not start, induction was considered to have failed and emergency caesarean section was offered. All women were sedated with intravenous diazepam and slow boluses of intravenous hydralazine if diastolic blood pressure was above 110 mmHg.

Misoprostol failure was recorded in four of 25 women (16%) and they were subsequently delivered by caesarean section. The mean duration of admission was statistically significantly longer in the caesarean section group (10.1 days versus 6.08 days; $P = 0.05$; no SD reported). There were no more maternal complications in the caesarean section group (eight of 25 versus two of 25: RR 4.0; 95% CI 0.94 to 17.00). Apgar scores at 1 minute and 5 minutes, babies' admission to NICU, perinatal mortality and maternal mortality did not differ statistically significantly between the groups.

A retrospective cohort study in the USA looked at outcomes of infants born after labour induction compared with those delivered by caesarean section without labour.[194] [EL = 2+] The study included 278 liveborn very low birthweight (750–1500 g) infants ($n = 145$ labour induction, $n = 133$ caesarean section without labour) delivered for women who had severe pre-eclampsia. Women received intramuscular magnesium sulphate for seizure prophylaxis and intravenous hydralazine for severe hypertension. No glucocorticoids were given for fetal lung maturation. Baseline characteristics for the women in the two groups were statistically significantly different in terms of age and nulliparity.

Both birthweight and gestational age were statistically significantly lower in the caesarean section group (birthweight: 1131 ± 232 g versus 1235 ± 185 g; $P = 0.001$, gestational age: 29.9 ± 2.3 weeks versus 30.8 ± 2.6 weeks; $P = 0.004$). After adjustment for birthweight and gestational age, logistic regression analysis showed the OR for Apgar score less than or equal to 3 at 5 minutes to be statistically significantly different (induction group: OR 6.1; 95% CI 1.1 to 32.2). The ORs for umbilical artery blood pH less than or equal to 7.0, respiratory distress syndrome, sepsis, intraventricular haemorrhage, seizures and neonatal deaths were not statistically significant.

Vaginal birth versus caesarean section after labour induction

An chart review study in the USA investigated outcomes of 306 women who underwent elective caesarean section ($n = 161$), caesarean section after labour induction ($n = 75$) and vaginal delivery after labour induction ($n = 70$).[195] [EL = 3] Participants were women who had severe pre-eclampsia and with single liveborn babies (24–34 weeks of gestation). Maternal age, parity and gestational age at delivery were comparable between the groups.

No statistically significant differences were found after induction between caesarean section and vaginal delivery in Apgar score less than 7 at 5 minutes or endometritis. Total hospital stay was also no different between the two groups but, after excluding three women who had an unusually prolonged hospital stay (longer than 400 hours) for unrelated medical conditions (SLE nephritis in two women and sickle cell disease in the third), total hospital stay became statistically significantly higher in the caesarean section group (130.0 ± 41.1 hours versus 109.7 ± 44.3 hours; $P = 0.005$).

Evidence statement

When comparing caesarean section without labour with labour induction, an RCT [EL = 1−] showed no statistically significant difference in reported maternal or neonatal complications. However, women allocated to caesarean section stayed for statistically significantly longer periods in the hospital. A retrospective cohort study [EL = 2+] showed odds for Apgar score less than or equal to 3 at 5 minutes to be statistically significantly lower in the caesarean section group. However, the odds for neonatal complications including umbilical artery blood pH less than or equal to 7.0, respiratory distress syndrome, sepsis, intraventricular haemorrhage, seizures and neonatal deaths were not statistically significant.

When comparing vaginal birth after labour induction with caesarean section after labour induction, a chart review study [EL = 3] showed no difference between the two groups in

reported outcomes (Apgar score less than 7 at 5 minutes and endometritis). Hospital stay, however, was statistically significantly longer in those who underwent caesarean section.

GDG interpretation of the evidence

Poor-quality small studies seemed to indicate little advantage to caesarean section and in one study women undergoing caesarean section had longer postnatal stays. However, it was felt that flaws in the studies available meant that there were no reliable data to inform the GDG and it was felt that mode of delivery would be best decided on both clinical circumstance and the woman's preference.

Recommendation

Choose mode of birth for women with severe hypertension, severe pre-eclampsia or eclampsia according to the clinical circumstances and the woman's preference.

10.8 Indications for referral to critical care levels

There are no studies into specific indications for care of women with severe hypertensive disorders during pregnancy in specific critical care settings.

The GDG has adapted existing definitions and guidance for critical care produced by the Intensive Care Society to reflect the range of disease severity in pre-eclampsia and gestational hypertension.

Recommendation

Offer women with severe hypertension or severe pre-eclampsia referral to the appropriate critical care setting using the following criteria:[‡]

Level 3 care	• Severe pre-eclampsia and needing ventilation
Level 2 care	Step-down from level 3 or severe pre-eclampsia with any of the following complications: • eclampsia • HELLP syndrome • haemorrhage • hyperkalaemia • severe oliguria • coagulation support • intravenous antihypertensive treatment • initial stabilisation of severe hypertension • evidence of cardiac failure • abnormal neurology
Level 1 care	• Pre-eclampsia with mild or moderate hypertension • Ongoing conservative antenatal management of severe preterm hypertension • Step-down treatment after the birth

[‡] Adapted from Intensive Care Society, Standards and Guidelines 2002.

11 Breastfeeding

11.1 Introduction

Breastfeeding is the feeding method of choice and encouraging breastfeeding is a key priority for maternity care providers (whether working in hospital or in primary care; see 'Postnatal care', NICE clinical guideline 37).[29] While hypertension is not in itself a contraindication to breastfeeding, the compatibility of antihypertensive drugs with breastfeeding may be an issue for discussion between women with hypertensive disorders and their healthcare providers. In this section, the GDG sought to identify evidence in relation to the safety of antihypertensive agents during breastfeeding.

11.2 Antihypertensive agents and breastfeeding

Clinical effectiveness

No clinical studies were identified in relation to the compatibility of antihypertensive drugs and breastfeeding (that is, in terms of adverse effects on babies whose mothers were taking antihypertensive agents while breastfeeding). However, a number of studies reported non-clinical outcomes (such as excretion of particular drugs in breast milk or detection in maternal or infant blood plasma). These studies are summarised in Table 11.1. Further details (including data for other antihypertensive drugs) are provided in Appendices M and N.

Evidence statement

No clinical studies were identified in relation to the compatibility of antihypertensive drugs and breastfeeding. A number of studies reported that the following drugs were excreted in breast milk of women who were taking antihypertensives or were detected in maternal or infant blood plasma:

- methyldopa (centrally acting; quantities too small to be harmful)
- the beta-blockers labetalol, propranolol, atenolol and metoprolol (small quantities detected in each case)
- the calcium-channel blockers nifedipine (small quantity detected) and verapamil (quantity too small to be harmful)
- the ACE inhibitors enalapril and captopril (data on maternal blood plasma concentrations only)
- the vasodilator hydralazine
- the thiazide diuretics hydrochlorothiazide, chlorothiazide and chlortalidone.

Table 11.1 Summary of studies evaluating the safety of antihypertensives commonly used during breastfeeding

	Study	No. of women	Dose used	Steady-state level		Milk : plasma ratio	Effect on babies	Relative infant dose	Reported paediatric concerns	Comments
				Serum or plasma	Milk					
Centrally acting										
Methyldopa	White *et al.* (1985)[196] USA	3	500–1000 mg/day orally	1.02 ± 0.93 micrograms/ml	0.225 ± 0.199 micrograms/ml	0.22	In two of the three breastfed babies, plasma levels were undetectable (< 0.05 micrograms/ml) 6 hours after administration of the drug, but in one baby plasma concentration was 0.09 micrograms/ml 10 hours after maternal dosing. It is estimated that when the mother receives 1 mg methyldopa a day, the average cumulative load to the breastfed baby would be 195 micrograms a day, or 20% of the maternal dose	0.11[197]	None[197;198]	Amount too small to be harmful[199]
	Hauser *et al.* (1985)[200] Israel	1	250 mg (×1)	2.5 hours after dose: 1430 ng/ml	2.5 hours after dose: < 200 ng/ml	–	No adverse clinical effects were noted during the 3-month follow-up period of the baby. Methyldopa is excreted in human milk in concentrations that probably do not harm the breastfed baby			
Beta-blockers										
Labetalol	Lunell *et al.* (1985)[201] Sweden	3	600–1200 mg/day	228 ± 178 micrograms/litre	220 ± 253 micrograms/litre	1.5	No consistent pattern in the milk : plasma ratio. There was a measurable plasma concentration in one baby. At the end of the dose interval, the concentration was similar to that in the mother.	0.57%[197]	None[197;202]	Only small quantities are excreted into breast milk[197;202]
Propranolol	Taylor *et al.* (1981)[203] UK	1	20 mg twice a day	2.25 hours after last dose: 17 ng/ml	2.25 hours after last dose: 4 ng/ml	0.24	Estimated intake of propranolol by infants was 3 micrograms/day	0.28%[197] 0.4%[198]	None[197]	Monitor for symptoms of beta-blockade[202] The amount in breast milk is low[197] The American Academy of Paediatrics classifies it as compatible with breastfeeding[202] Long-term effects on babies are not known[202]
				3.25 hour after last dose: 16 ng/ml	3.25 hour after last dose: 11 ng/ml	0.69				
	Smith *et al.* (1983)[204] Australia	3	40 mg four times a day	711 ± 49 ng/ml (peak)	429 ± 28 ng/ml (peak)	0.60	None (30 day follow-up for baby)			
	Bauer *et al.* (1979)[205] USA	9	20 mg twice a day	17 ng/ml (peak)	4 ng/ml (peak)	0.24	No changes in heart rate			
	Thorley *et al.* (1983)[206] UK	5	40 mg twice a day	2 hours after dose: 54 ± 14 ng/ml	2 hours after dose: 27 ± 5 ng/ml	2.0	None of the babies showed any clinical signs of beta-blockade			

Table 11.1 *(continued)* Summary of studies evaluating the safety of antihypertensives commonly used during breastfeeding

	Study	No. of women	Dose used	Steady-state level		Milk : plasma ratio	Effect on babies	Relative infant dose	Reported paediatric concerns	Comments
				Serum or plasma	Milk					
Beta-blockers (continued)										
Atenolol	White *et al.* (1984)[207] USA	8	50 mg	0.36 micrograms/ml	1.3 micrograms/ml	3.6	Level in infant plasma undetectable (< 10 ng/ml); no bradycardia or lethargy	6.6%[197]	One reported case of bradycardia, cyanosis and hypothermia required hospitalisation[197;198;202]	Monitor for symptoms of beta-blockade[202] Some authors failed to detect atenolol in breast milk[197] Possible significant transfer to baby and accumulation in preterm babies
	Liedholm *et al.* (1981)[208] Sweden	1	100 mg	0.62 micrograms/ml (peak)	1.8 micrograms/ml (peak)	2.9	–			
	Thorley *et al.* (1983)[206] UK	5	100 mg/day	2 hours after dose: 712 ± 77 ng/ml	2 hours after dose: : 630 ± 121 ng/ml	1.3	None of the babies showed any clinical signs of beta-blockade			
	Kulas *et al.* (1984)[209] Sweden	4	100 mg (×1)	1658 ± 531 nmol/litre	3512 ± 848 nmol/litre	2.11	–			
	Schimmel *et al.* (1989)[210] Canada and Israel	1	50 mg twice a day		1.5 hour after dose: 469 ng/ml	–	–			
Meto-prolol	Kulas *et al.* (1984)[209] Sweden	3	100 mg (×1) or 50 mg (×2)	99 ± 37 nmol/litre	281 ± 103 nmol/litre	2.83	–	1.4%[197]	Nil[197;202]	Maternal plasma levels are small and so infant dose remains low[197]
Calcium-channel blockers										
Nifedipine	Manninen *et al.* (1991)[211] Finland	11	10 mg three times a day	12.04 ± 4.0 ng/ml	4.1 ± 0.8 ng/ml	0.34	–	1.8[197]		Amount too small to be harmful, but manufacturer suggests avoid[199;202]
	Penny *et al.* (1989)[212] UK	1	20 mg	43 ng/ml (peak)	46 ng/ml (peak)	1.07	No babies studied			
Verapamil	Anderson *et al.* (1987)[213] Sweden	1	80 mg three times a day	42.9 ng/ml	25.8 ng/ml	0.60	The ratio between the total dose of verapamil to which the breastfed baby was exposed and that given to the mother in 24 hours was 0.0001, so the baby received at most 0.01% of the dose of verapamil given to the mother. No verapamil (< 1 ng/ml) was found in the baby's plasma	0.15–0.98%[197]	Nil[197;202]	Amount too small to be harmful,[199] although the relevant SPCs state that verapamil is excreted into the breast milk in small amounts and is unlikely to be harmful, but that rare hypersensitivity reactions have been reported with verapamil and therefore it should only be used during lactation if, in the clinician's judgement, it is essential for the welfare of the patient

Table 11.1 *(continued)* Summary of studies evaluating the safety of antihypertensives commonly used during breastfeeding

	Study	No. of women	Dose used	Steady-state level		Milk : plasma ratio	Effect on babies	Relative infant dose	Reported paediatric concerns	Comments
				Serum or plasma	Milk					
Angiotensin-converting enzyme (ACE) inhibitors										
Enalapril	Redman *et al.* (1990)[214] UK and Ireland	5	20 mg orally (×1)	123 ± 28 ng/ml (peak)	1.74 ± 2.41 ng/ml (peak)	0.014	No babies	0.17%[197]	Nil[197]	Manufacturer suggests avoid[199] Can be used in breastfeeding when first-choice agents cannot be used or are ineffective (with monitoring)[197]
Captopril	Devlin *et al.* (1981)[215] USA	12	100 mg three times a day (7 doses)	133.4 ng/ml 713.1 ± 140.6 ng/ml (peak)	2.9 ng/ml 4.7 ± 0.7 ng/ml (peak)	0.02 0.01 (peak)	Babies not studied, data suggest that the human breast selectively restricts the passage of captopril from blood into milk	0.02%[197]	None[197;202]	Manufacturer suggests avoid[199] Can be used in breastfeeding when first choice agents cannot be used or are ineffective (with monitoring)[197]
Vasodilators										
Hydralazine	Liedholm *et al.* (1982)[216] Sweden	1	50 mg three times a day	2 hours after a.m. dose: 580 nmol/litre (active hydralazine)	2 hours after a.m. dose: 792 nmol/litre (active hydralazine)	1.4	Even if all hydralazine in the milk comprised active hydralazine and assuming a normal feeding volume of 75 ml milk, the calculated dose would not exceed 0.013 mg per feed, i.e. a negligible amount	1.2%[197]	None[197;198;202]	Present in milk but not known to be harmful[199]
				½ hour after midday dose: 1535 nmol/litre (active hydralazine)	½ hour after midday dose: 762 nmol/litre (active hydralazine)	0.5				
Thiazide diuretics										
Hydrochloro-thiazide	Miller *et al.* (1982)[217] USA	1	50 mg	280 ng/ml (peak)	120 ng/ml (peak)	0.43	No detectable levels (< 1 ng/ml); electrolytes normal in baby	–	–	–
Chloro-thiazide	Werthmann *et al.* (1972)[218] USA	11	500 mg (×1)	< 1 micrograms/ml	< 1 micrograms/ml	–	No babies studied	–	–	–
Chlortalidone	Mulley *et al.* (1978)[219] USA	7	50 mg	6.54 ± 1.86 micrograms/ml (peak)	0.37 ± 0.27 micrograms/ml (peak)	0.06	No babies studied	15.5%[198]	Nil[198]	Amount too small to be harmful[199] The American Academy of Paediatrics classifies it as compatible with breastfeeding[202]

GDG interpretation of the evidence

The GDG is aware of an MHRA newsletter (May 2009 issue of the MHRA *Drug Safety Update*, available at www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON046451) that identifies methyldopa as the antihypertensive of choice during breastfeeding. However, the MHRA *Drug Safety Update* does not reflect the association between methyldopa and clinical depression, and the GDG's view is that methyldopa should not be used in the postnatal period because women are already at risk of depression at this time (see Section 4.8). The MHRA *Drug Safety Update* notes that 'ACE inhibitors have a small molecular size and so their transfer to breast milk is possible. Data on the use of ACE inhibitors in breastfeeding are sparse and relate mostly to captopril, enalapril, and quinapril; findings indicate that drug is transferred to breast milk. Although the levels transferred to an infant via breastfeeding are unlikely to be clinically relevant, there are insufficient data to exclude a possible risk of profound neonatal hypotension, particularly in preterm babies.' The MHRA *Drug Safety Update* draws on exactly the same studies considered by the GDG in relation to enalapril and captopril (see Table 11.1) but reaches a different interpretation of the evidence. Neither of the studies considered in relation to enalapril and captopril provided data on infant outcomes (such as blood plasma concentrations of the drugs following breastfeeding, or adverse clinical outcomes). The evidence considered by the MHRA in relation to quinapril is not relevant to the current discussion as the GDG did not wish to recommend its use during breastfeeding.

The GDG noted that there is very little good evidence on the compatibility of antihypertensive drugs and breastfeeding, particularly for clinical outcomes, and that most of the commonly used antihypertensive drugs appear to be safe for the baby (including labetalol, nifedipine and methyldopa, which are the drugs most likely to be used by women with gestational hypertension). The consensus view of the GDG was that the benefits to the mother and the baby of breastfeeding (and/or the baby receiving the mother's expressed breast milk) far outweigh potential risks to the baby of transfer of antihypertensive drugs in breast milk. The GDG noted that if ACE inhibitors were needed during the postnatal period then enalapril and captopril were the recommended drugs in this class (because of the quality and quantity of associated safety data), even though they are not used widely outside pregnancy.

The GDG also reflected on the risk of neonatal hypoglycaemia or poor establishment of feeding in babies born to women with hypertensive disorders during pregnancy (owing to the increased risk of being born preterm (including some who would be born at 34–36 weeks), SGA or exposed to antihypertensive drugs antenatally). Such babies will require a period of clinical monitoring (possibly including blood glucose monitoring) and assessment of adequacy of feeding). In these circumstances, the woman should be advised that she and the baby are likely to need to stay in hospital for at least 48 hours after the birth to ensure adequacy of feeding and prevention of hypoglycaemia before discharge. Thus guidance about how long a mother needs to stay in hospital should take into account both the mother's and baby's wellbeing. Detailed recommendations for postnatal care of the baby are outside the scope of this guideline, but the GDG's view is that the baby's wellbeing and adequacy of feeding should be assessed at least daily for the first 2 days after the birth. The GDG's recommendations in relation to the drugs to use during breastfeeding are consistent with the recommended framework for monitoring of the baby. The GDG also highlighted the potential benefits of offering parents information and advice to enable them to assess their baby's general condition and to identify signs and symptoms of common health problems seen in babies and how to contact a healthcare professional or emergency service if required (see 'Postnatal care', NICE clinical guideline 37).[29]

Recommendations

In women who still need antihypertensive treatment in the postnatal period, avoid diuretic treatment for hypertension if the woman is breastfeeding or expressing milk.

Tell women who still need antihypertensive treatment in the postnatal period that the following antihypertensive drugs have no known adverse effects on babies receiving breast milk:

- labetalol†
- nifedipine†
- enalapril†
- captopril†
- atenolol†
- metoprolol.†

Tell women who still need antihypertensive treatment in the postnatal period that there is insufficient evidence on the safety in babies receiving breast milk of the following antihypertensive drugs:

- ARBs
- amlodipine
- ACE inhibitors other than enalapril† and captopril.†

Assess the clinical wellbeing of the baby, especially adequacy of feeding, at least daily for the first 2 days after the birth.

Research recommendation

How safe are commonly used antihypertensive agents when used by women who are breastfeeding?

Why this is important

With the increasing incidence of hypertensive disorders during pregnancy, more pregnant and breastfeeding women will potentially be exposed to antihypertensive medication. Most of the relevant drugs are not licensed for use in pregnancy. For most drugs there is no information on their presence in human breast milk, or if such a presence has any clinical effect. As a result, women may either be denied effective treatment in the postnatal period or advised against breastfeeding. Studies should measure the concentration of relevant drugs and their metabolites in breast milk, taking account of drug pharmacokinetics (peak levels and elimination) and comparing neonatal behaviour and physiological variables in women using each drug with those in women who choose not to breastfeed. Studies should follow women and their babies for long enough to exclude cumulative effects and they should be large enough to provide reassurance to licensing and drug regulating authorities.

† This guideline assumes that prescribers will use a drug's summary of product characteristics (SPC) to inform decisions made with individual patients. Drugs for which particular attention should be paid to the contraindications and special warnings during pregnancy and lactation are marked with † and detailed in Section 1.6.

12 Advice and follow-up care at transfer to community care

12.1 Introduction

The development of new hypertension during pregnancy will have had an impact on the woman's experience of the pregnancy itself. Particularly if severe, it will have raised concerns about the woman's future health and the prospects for a further pregnancy. Women will wish to discuss the events surrounding the pregnancy and learn whether there are lifestyle changes or therapies that would avoid or reduce the risk of a further pregnancy being complicated by hypertension.

This chapter presents recommendations on the advice women should receive before discharge from the maternity services concerning long-term risks and also about preparation and risks for a further pregnancy.

12.2 Long-term risk of cardiovascular disease

Clinical effectiveness

Two systematic reviews were identified that investigated the long-term risks of cardiovascular events.

One review by Bellamy *et al.*[21] [EI = 1++] investigated the association between pre-eclampsia and atherosclerosis in later life. The review looked at prospective and retrospective cohort studies assessing women of any parity or age with any severity of pre-eclampsia. Case–control studies were excluded. Included cohort studies provided a set of 3 488 160 women, with 198 252 affected by pre-eclampsia. Pre-eclampsia was defined as the onset of a blood pressure level exceeding 140/90 mmHg with proteinuria above 300 mg/24 hours.

A second review, by McDonald *et al.*,[220] [EL = 1++] assessed the long-term (more than 6 weeks postpartum) cardiovascular sequelae of pre-eclampsia/eclampsia. Both case–control and cohort studies were examined, of which five case–control studies and ten cohort studies were finally included (the total number of women was 2 259 576, with 118 990 of those having a history of pre-eclampsia/eclampsia). The reviewers judged that adjustment for the following variables was appropriate: age, and other traditional cardiovascular risk factors (hypertension, hyperlipidaemia, diabetes or impaired glucose tolerance, family history of cardiovascular disease, and smoking).

The various cardiovascular outcomes studied are listed below and the results are summarised in Table 12.1.

Risk of future hypertension

The review by Bellamy *et al.*[21] included 13 studies (21 030 women); 1885 of the 3658 women who had had pre-eclampsia developed chronic hypertension in later life. The mean weighted follow-up was 14.1 years. Women who had had pre-eclampsia were at a statistically significant higher risk of developing hypertension (RR 3.70; 95% CI 2.70 to 5.05) compared with those who had not developed pre-eclampsia. However, significant heterogeneity was observed ($P = 0.001$; $I^2 = 62.6\%$), with evidence that small studies reported larger effect sizes (Egger test,

$P = 0.014$). In analyses stratified according to the total number of cases, a smaller risk for hypertension (RR 2.37; 95% CI 2.11 to 2.66) was obtained after pooling the two large studies, each with more than 200 cases, compared with the risk from pooling 11 small studies, each with fewer than 200 cases (RR 4.43; 95% CI 3.24 to 6.05).

Analysis according to parity indicated a higher relative risk of hypertension after pre-eclampsia in any pregnancy (four studies: RR 5.96; 95% CI 3.42 to 10.38) compared with pre-eclampsia in the first pregnancy only (nine studies: RR 3.23; 95% CI 2.32 to 4.52) ($\chi^2 = 8.48$; $P = 0.004$).

Risk of ischaemic heart disease

The review by Bellamy *et al.*[21] included eight studies (2 346 997 women); 5097 women of the 121 487 who had had pre-eclampsia developed ischaemic heart disease events. The weighted mean follow-up was 11.7 years.

The relative risk of fatal or non-fatal ischaemic heart disease in women with previous pre-eclampsia was over twice that of women who had not developed pre-eclampsia (RR 2.16; 95% CI 1.86 to 2.52). No significant heterogeneity was observed ($P = 0.21$; $I^2 = 27.1\%$). The Egger regression test showed no evidence of small-study bias ($P = 0.59$). Subgroup analysis by parity showed no statistically significant difference between primiparous women who had had pre-eclampsia and women who had had pre-eclampsia in any pregnancy. The risk of future fatal ischaemic heart disease events was statistically significantly increased in women after pre-eclampsia (four studies: RR 2.60; 95% CI 1.94 to 3.49).

In two studies, pre-eclampsia before 37 weeks was associated with nearly an eight-fold increased risk of ischaemic heart disease (RR 7.71; 95% CI 4.40 to 13.52) compared with women with normal blood pressure completing pregnancies after 37 weeks.

The severity of pre-eclampsia also increased the risk of later ischaemic heart disease but not to the same extent as the gestation of onset. Two studies showed that women who had had severe pre-eclampsia (blood pressure of 160/110 mmHg or higher plus proteinuria above 300 mg/24 hours or diastolic blood pressure of 110 mmHg or higher plus proteinuria above 5 g/24 hours) were at greater risk of later ischaemic heart disease (RR 2.86; 95% CI 2.25 to 3.65) than were women who had had mild pre-eclampsia (RR 1.92; 95% CI 1.65 to 2.24).

The review by McDonald *et al.*[220] showed that, relative to women with uncomplicated pregnancies, women with a history of pre-eclampsia/eclampsia had a statistically significantly increased risk of subsequent cardiac disease in both the four case–control studies (OR 2.47; 95% CI 1.22 to 5.01) and the ten cohort studies (RR 2.33; 95% CI 1.95 to 2.78).

Meta-regression revealed a graded relationship between the severity of pre-eclampsia/eclampsia and the risk of cardiac disease as follows: mild pre-eclampsia (RR 2.00; 95% CI 1.83 to 2.19), moderate pre-eclampsia (RR 2.99; 95% CI 2.51 to 3.58) and severe pre-eclampsia (RR 5.36; 95% CI 3.96 to 7.27); $P < 0.0001$. The results were homogeneous across each of the categories of risk ($I^2 = 0\%$ for each category).

Risk of cerebrovascular accident

The review by Bellamy *et al.*[21] included four studies (1 671 578 women) that looked at the risk of CVAs in women who had had pre-eclampsia. Nine hundred and seven women of the 64 551 who had had pre-eclampsia developed CVAs. The mean weighted follow-up was 10.4 years. The overall risk of fatal and non-fatal CVA after pre-eclampsia was 1.81 (95% CI 1.45 to 2.27) compared with women who had not developed pre-eclampsia. No heterogeneity was observed ($P = 0.51$; $I^2 = 0\%$) and no evidence of small-study bias was found (Egger test, $P = 0.82$). Subgroup analysis showed that the risk of fatal CVA (two studies: RR 2.98; 95% CI 1.11 to 7.96) was greater than that of non-fatal CVA after pre-eclampsia (two studies: RR 1.76, 1.40 to 2.22).

A diagnosis of pre-eclampsia before 37 weeks was associated with a higher risk of CVA in later life (RR 5.08; 95% CI 2.09 to 12.35) than was a diagnosis of pre-eclampsia after 37 weeks (RR 0.98; 95% CI 0.50 to 1.92).

In the review by McDonald *et al.*,[220] the single eligible case–control study that examined the risk of cerebrovascular disease reported an increased risk (OR 2.6; 95% CI 1.5 to 4.3), in keeping with the pooled estimate in the results from six cohort studies (RR 2.03; 95% CI 1.54 to 2.67).

Pre-eclampsia and risk of venous thromboembolism

The review by Bellamy *et al.*[21] included three studies (427 693 women); 470 women out of the 35 772 who had had pre-eclampsia developed venous thromboembolism. The weighted mean follow-up was 4.7 years. The relative risk of venous thromboembolism in women who developed pre-eclampsia was 1.79 (95% CI 1.37 to 2.33) compared with women who had not developed pre-eclampsia. No heterogeneity was observed ($P = 0.65$; $I^2 = 0\%$). In one study, severe pre-eclampsia was associated with a higher risk of venous thromboembolism in later life (RR 2.3; 95% CI 1.3 to 4.2) than was mild pre-eclampsia (RR 1.4; 95% CI 0.9 to 2.2).

Risk of peripheral arterial disease

In the review by McDonald *et al.*,[220] cohort studies demonstrated that women who had had pre-eclampsia/eclampsia had a non-statistically significant trend toward an increased risk of subsequent peripheral arterial disease (three cohort studies: RR 1.87; 95% CI 0.94 to 3.73).

Risk of cardiovascular mortality

Pooled estimates from five cohort studies in the review by McDonald *et al.*[220] showed that women with a history of pre-eclampsia/eclampsia had a statistically significantly higher relative risk of dying of cardiovascular disease (RR 2.99; 95% CI 1.73 to 3.04).

Women with gestational hypertension

The review by Bellamy *et al.*[21] included two studies, totalling 2106 women, that investigated the association between a history of pregnancy-induced hypertension and future hypertension; 454 women had had pregnancy-induced hypertension and 300 incident cases of hypertension occurred within 10.8 years. The relative risk of incident hypertension for women who had had pregnancy-induced hypertension compared with women who had not was 3.39 (95% CI 0.82 to 13.92; P for heterogeneity = 0.0006; $I^2 = 91.4\%$). The increase in risk for future cardiovascular disease was 1.66 (95% CI 0.62 to 4.41; P for heterogeneity = 0.10; $I^2 = 63.8\%$).

Evidence statement

One systematic review of cohort studies [EL = 1++] and another one of cohort and case–control studies [EL = 1++] investigated the association between pre-eclampsia/eclampsia and atherosclerosis in later life. Women who had had pre-eclampsia were at higher risks of developing cardiovascular events in later life.

GDG interpretation of the evidence

The evidence on the long-term risk to women who have had pre-eclampsia is of good quality, with less information being available on the long-term consequences of gestational hypertension.

Women who have had pre-eclampsia have a lifelong increased risk of hypertension and its consequences. However, what is not clear is if pre-eclampsia is the cause of an increased risk for women who have hypertensive disorders or is part of the hypertensive disorder pathway. This risk appears greatest when pre-eclampsia presents before 37 weeks and there appears to be a gradation of risk by severity of hypertension. For gestational hypertension the magnitude of risk is similar, but because there are fewer studies the long-term impact remains uncertain, with less justification at present to advise these women of increased risk.

Table 12.1 Summary of evidence from systematic reviews for the risk of long-term cardiovascular disease after pre-eclampsia/eclampsia

	Studies in pool estimate	Population	RR (95% CI)	Mean follow-up (years)	Other factors related
Hypertension	13 cohort	Pre-eclampsia	3.70 (2.70 to 5.05)	14.1	The risk associated with previous pre-eclampsia in any pregnancy was higher than the risk associated with pre-eclampsia in the first pregnancy only
Ischaemic heart disease	8 cohort	Pre-eclampsia	2.16 (1.86 to 2.52)	11.7	The risk associated with previous pre-eclampsia before 37 weeks was higher than the risk associated with pre-eclampsia after 37 weeks The risk associated with severe previous pre-eclampsia was higher than that associated with moderate pre-eclampsia, which was in turn higher than that associated with mild pre-eclampsia
	10 cohort	Pre-eclampsia/ eclampsia	2.33 (1.95 to 2.78)		
	4 case–control	Pre-eclampsia/ eclampsia	OR 2.47 (1.22–5.01)		
Cerebrovascular accident (CVA)	4 cohort	Pre-eclampsia	1.81 (1.45 to 2.27)	10.4	The risk of fatal CVA was higher than the risk of non-fatal CVA The risk after previous pre-eclampsia before 37 weeks was higher than that associated with pre-eclampsia after 37 weeks
	6 cohort	Pre-eclampsia/ eclampsia	2.03 (1.54 to 2.67)		
	1 case–control	Pre-eclampsia/ eclampsia	OR 2.6 (1.5 to 4.3)		
Venous thromboembolism	3 cohort	Pre-eclampsia	1.79 (1.37 to 2.33)	4.7	The risk associated with previous severe pre-eclampsia was higher than that associated with mild pre-eclampsia
Peripheral arterial disease	3 cohort	Pre-eclampsia/ eclampsia	1.87 (0.94 to 3.73)		
Mortality of cardiovascular disease	5 cohort	Pre-eclampsia/ eclampsia	2.99 (1.73 to 3.04)		

Although the impact of informing women that they may have an increased long-term risk has not been studied, the evidence suggests that a previous history of pre-eclampsia puts the woman at an increased risk for subsequent cardiovascular disease. Increased surveillance in this group may lead to earlier intervention, usually with antihypertensives, with likely benefits for the woman. However, the GDG found insufficient evidence to support recommendations on the frequency of follow up (including blood pressure monitoring) for women who have had gestational hypertension or pre-eclampsia.

Recommendation

Tell women who have had gestational hypertension or pre-eclampsia, and their primary care clinicians, that these conditions are associated with an increased risk of developing high blood pressure and its complications in later life.

Research recommendation

What is the long-term outcome of women with gestational hypertension?

Why this is important

Long-term follow-up of women with pre-eclampsia has shown a lifetime increased risk of serious cardiovascular complications such as stroke. Gestational hypertension is much more common than pre-eclampsia. Studies following this group of women are very limited and are not robust enough to give clear advice.

Prospective or registry studies of the long-term consequences of gestational hypertension (both isolated and recurrent) should be carried out. Outcomes should include development of hypertension, ischaemic heart disease and stroke. Studies should determine co-risk factors, particularly those amenable to intervention. Randomised controlled trials of interventions (both lifestyle and pharmacological) similar to those carried out in people considered at risk of developing type 2 diabetes, should be considered if prospective studies demonstrate significant lifetime risks.

12.3 Long-term risk of end-stage kidney disease

Clinical effectiveness

A large retrospective cohort study conducted in Norway looked at the association between pre-eclampsia in one or more pregnancies and the subsequent risk of end-stage kidney disease.[221] [EL = 2++] The study population consisted of 570 433 women who had given birth to at least one child with a gestational age of 16 weeks or more; 480 006 of these women gave birth to a second child and 210 660 to a third child. The mean (±SD) durations of follow-up after the first, second and third pregnancies were 26.5 ± 7.5 years, 22.8 ± 0.8 years and 18.7 ± 8.2 years, respectively. The mean ages of the mother at the first, second and third deliveries were 23.5 ± 4.3 years, 26.9 ± 4.3 years and 30.2 ± 4.3 years, respectively.

End-stage kidney disease developed in 477 of 570 433 women a mean of 17 ± 9 years after the first pregnancy (overall rate 3.7 per 100 000 women per year). Among women who had been pregnant one or more times, pre-eclampsia during the first pregnancy was associated with a relative risk of end-stage kidney disease of 4.7 (95% CI 3.6 to 6.1) (Table 12.2). Among women who had been pregnant two or more times, pre-eclampsia during the first pregnancy was associated with a relative risk of end-stage kidney disease of 3.2 (95% CI 2.2 to 4.9), pre-eclampsia during the second pregnancy with a relative risk of 6.7 (95% CI 4.3 to 10.6), and pre-eclampsia during both pregnancies with a relative risk of 6.4 (95% CI 3.0 to 13.5). Among women who had been pregnant three or more times, pre-eclampsia during one pregnancy was associated with a relative risk of end-stage kidney disease of 6.3 (95% CI 4.1 to 9.9), and pre-eclampsia during two or three pregnancies was associated with a relative risk of 15.5 (95% CI 7.8 to 30.8).

Table 12.2 Summary of evidence for the risk of end-stage kidney disease after pre-eclampsia

Variable	Total no. of women	No. with end-stage kidney disease	No./100 000 person-year (95% CI)[a]	Adjusted relative risk (95% CI)[b]
After first pregnancy (all women)				
No pre-eclampsia	549 515	410	3.3 (2.9–3.6)	
Pre-eclampsia	20 918	67	14.5 (11.2–18.1)	4.3 (3.3–5.6)
After two pregnancies (women with ≥2 pregnancies)				
No pre-eclampsia	456 884	266	2.8 (2.5–3.1)	
Pre-eclampsia in first pregnancy only	14 588	25	8.6 (5.6–12.3)	3.1 (2.0–4.7)
Pre-eclampsia in second pregnancy only	6 120	20	16.8 (10.3–25.0)	5.3 (3.3–8.5)
Pre-eclampsia in both pregnancies	2 411	7	15.4 (6.1–29.0)	4.7 (2.1–10.7)
After three pregnancies (women with ≥3 pregnancies)				
No pre-eclampsia	198 192	84	2.4 (1.9–2.9)	
Pre-eclampsia in one pregnancy only	10 727	26	14.4 (9.4–20.5)	5.8 (3.7–9.1)
Pre-eclampsia in first pregnancy only	5 930	6	6.0 (2.1–11.7)	2.6 (1.1–5.9)[c]
Pre-eclampsia in second pregnancy only	1 875	5	16.2 (5.1–33.4)	7.3 (3.0–18.1)[c]
Pre-eclampsia in third pregnancy only	2 922	15	30.6 (17.1–48.1)	14.3(8.2–24.7)[c]
Pre-eclampsia in ≥2 pregnancies	1 741	9	32.9 (14.9–57.9)	10.9 (5.0–23.8)

Separate analyses setting the baseline at 10 years after the pregnancy of interest confirmed a statistically significant association between pre-eclampsia and end-stage kidney disease. These analyses showed that after one pregnancy with pre-eclampsia, the relative risk of end-stage kidney disease was 4.1 (95% CI 3.1 to 5.5); after two pregnancies, the relative risk of end-stage kidney disease was 3.1 (95% CI 2.0 to 4.9) for pre-eclampsia in the first pregnancy, 6.1 (95% CI 3.6 to 10.3) for pre-eclampsia in the second pregnancy, and 5.7 (95% CI 2.3 to 13.7) for pre-eclampsia in both pregnancies; after three pregnancies, the relative risk was 5.8 (95% CI 3.5 to 9.6) for pre-eclampsia in one pregnancy and 6.7 (95% CI 2.1 to 21.3) for pre-eclampsia in two or more pregnancies. Further analyses showed that among women with three pregnancies, one of which was complicated by pre-eclampsia, the relative risk of end-stage kidney disease varied, depending on whether pre-eclampsia occurred during the first pregnancy (RR 2.6; 95% CI 1.1 to 5.9), the second pregnancy (RR 7.3; 95% CI 3.0 to 18.1) or the third pregnancy (RR 14.3; 95% CI 8.2 to 24.7). The associations between pre-eclampsia and end-stage kidney disease remained statistically significant after adjustment for potential confounders and after the exclusion of women who had received a diagnosis of diabetes mellitus, kidney disease, essential hypertension or rheumatic disease before the included pregnancies.

Evidence statement

A large retrospective cohort study [EL = 2++] showed that end-stage kidney disease developed in 477 of 570 433 women a mean of 17 ± 9 years after the first pregnancy (overall rate 3.7 per 100 000 women per year).

Evidence suggested that among women who had been pregnant one or more times, pre-eclampsia during the first pregnancy was associated with a relative risk of end-stage kidney disease of 4.7 (95% CI 3.6 to 6.1). Among women who had been pregnant two or more times, pre-eclampsia during the first pregnancy was associated with a relative risk of end-stage kidney disease of 3.2 (95% CI 2.2 to 4.9), pre-eclampsia during the second pregnancy with a relative risk of 6.7 (95% CI 4.3 to 10.6), and pre-eclampsia during both pregnancies with a relative risk of 6.4 (95% CI 3.0 to 13.5). Among women who had been pregnant three or more times, pre-eclampsia during one pregnancy was associated with a relative risk of end-stage kidney disease of 6.3 (95% CI 4.1 to 9.9), and pre-eclampsia during two or three pregnancies was associated with a relative risk of 15.5 (95% CI 7.8 to 30.8).

GDG interpretation of the evidence

The risk of end-stage kidney disease is increased in women who have had previous pre-eclampsia although the absolute risk remains low. Women with persistent proteinuria or hypertension or who have abnormal renal function discovered during pregnancies complicated by hypertension will make up a large proportion of this group.

The absolute risk is sufficiently low that no specific advice is necessary and no additional follow-up required.

Recommendation

Tell women with a history of pre-eclampsia who have no proteinuria and no hypertension at the postnatal review (6–8 weeks after the birth) that although the relative risk of kidney disease is increased the absolute risk is low and no further follow-up is necessary.

12.4 Thrombophilia and the risk of pre-eclampsia

Clinical effectiveness

An HTA report looked at screening for thrombophilia in high-risk pregnancies.[222] [EL = 1++] It assessed the risk of clinical complications, including pre-eclampsia, associated with thrombophilia.

All prospective and retrospective studies of venous thromboembolism events and thrombophilia in women taking oral estrogen preparations and patients undergoing major orthopaedic surgery and studies of venous thromboembolism events and adverse obstetric complications in women with thrombophilia during pregnancy were considered. Only relevant studies that reported categorical data relating to the presence and absence of thrombophilia were included. Odds ratios associated with individual clinical outcomes, stratified by thrombophilia type, were calculated for each patient group. Meta-analysis was conducted based on the random effects model.

Pooled data showed that pregnant women with hyperhomocysteinaemia are statistically significantly more likely to develop pre-eclampsia than women with other thrombophilias (OR 3.49; 95% CI 1.21 to 10.11). MTHFR homozygous, however, was associated with the lowest risk of pre-eclampsia (OR 1.32; 95% CI 1.05 to 1.66). Both anticardiolipin antibodies and prothrombin heterozygosity were statistically significantly associated with pre-eclampsia (OR 2.73; 95% CI 1.65 to 4.51 and OR 2.54; 95% CI 1.52 to 4.23, respectively).

While factor V Leiden homozygosity was not found as a statistically significant predictor of pre-eclampsia (OR 1.87; 95% CI 0.44 to 7.88), heterozygotes were at a statistically significantly higher risk of developing pre-eclampsia (OR 2.34; 95% CI 1.56 to 3.51).

None of the antithrombin III, protein C or protein S deficiencies was statistically significantly associated with pre-eclampsia. Similarly, neither lupus anticoagulants nor acquired activated protein C resistance (APCR) was found to put women at statistically significantly higher risk of developing pre-eclampsia.

In summary, women having some of the thrombophilias are at a statistically significantly higher risk of developing pre-eclampsia than those who do not have thrombophilias (688 of 1190 versus 6222 of 13985: OR 1.91; 95% CI 1.60 to 2.28).

Evidence statement

An HTA [EL = 1++] looking at thrombophilia and risk of pre-eclampsia showed that pregnant women with the thrombophilias outlined in Table 12.3 have higher odds of developing pre-eclampsia.

Table 12.3 Summary of evidence for the risk of pre-eclampsia with various thrombophilias

Thrombophilia	Odds ratio (95% CI)
Hyperhomocysteinaemia	3.49 (1.21 to 10.11)
Prothrombin heterozygous	2.73 (1.65 to 4.51)
Anticardiolipin antibodies	2.54 (1.52 to 4.23)
Factor V Leiden heterozygotes	2.34 (1.56 to 3.51)
MTHFR homozygous	1.32 (1.05 to 1.66)

The following thrombophilias were not found to be statistically significantly associated with pre-eclampsia:

- factor V Leiden homozygous
- antithrombin III deficiency
- protein C deficiency
- protein S deficiency
- lupus anticoagulants
- acquired APCR.

In summary, women having some of the thrombophilias are at a statistically significantly higher risk of developing pre-eclampsia than those who do not have thrombophilias (688 of 1190 versus 6222 of 13985: OR 1.91; 95% CI 1.60 to 2.28).

GDG interpretation of the evidence

The GDG considers that the evidence on the association between thrombophilias and hypertensive disorders remains unclear and is of variable quality. Even with an association, the value of routine screening for these disorders would be unclear as there is no good evidence that treatment (thromboprophylaxis or increased folate intake) improves outcomes related to hypertensive disorders in the next pregnancy or prevents disease occurrence. All of these women would be recommended to take aspirin. The question of whether such women should have thromboprophylaxis for venous thromboembolism is outside the scope of this guideline.

Recommendation

Do not routinely perform screening for thrombophilia in women who have had pre-eclampsia.

12.5 Risk of recurrence of hypertensive disorders of pregnancy

Clinical effectiveness

Previous pregnancy with gestational hypertension

Five retrospective cohort studies[223-227] [EL = 2+] investigated recurrence of hypertensive disorders of pregnancy in women who had had gestational hypertension in the index pregnancy. The studies were conducted in Iceland, Scotland, the USA and Australia (two studies). In two studies,[223;225] the index pregnancy was the first pregnancy and recurrence was investigated in the second pregnancy. In the other three studies,[224;226;227] the index pregnancy was not always first pregnancy and subsequent pregnancies were not always consecutive but only one subsequent pregnancy was included.

The risk of recurrence of gestational hypertension ranged between 16% and 47% in the various studies, as shown in Table 12.4. Recurrence of pre-eclampsia in a subsequent pregnancy ranged between 2% and 7%. The incidence of gestational hypertension after a normotensive index pregnancy was 9.3%.

Table 12.4 Summary of studies that presented the risk of recurrence of pregnancy-related hypertension in women with previous gestational hypertension

Study	No. of participants	Recurrence % (*n*)	
		Gestational hypertension	Pre-eclampsia
Hjartardottir *et al.* (2006), Iceland[223]	511	47% (240)	7% (36)
Brown *et al.* (2007), Australia[224]	367	26% (95)	3% (11)
Hargood *et al.* (1991), Australia[226]	121	44% (53)	2% (2)
Campbell *et al.* (1985), Scotland[225]	1339	29% (388)	2% (27)
Zhang *et al.* (2001), USA[227]	237	16% (38)	3% (7)

Previous pregnancy with pre-eclampsia

Nine retrospective cohort studies[14 223-230] [EL = 2+] investigated the recurrence of hypertensive disorders of pregnancy in women with pre-eclampsia in an index pregnancy. The studies were conducted in Iceland, Scotland, the USA (two studies), Australia (two studies), Norway, Denmark and Sweden. In six studies,[14 223;225;228-230] the index pregnancy was the first pregnancy and recurrence was investigated in the next (second) pregnancy. In the other three studies,[224;226;227] the index pregnancy was not always the first pregnancy and subsequent pregnancies were not always consecutive but only one subsequent pregnancy was included.

The risk of gestational hypertension in a subsequent pregnancy ranged from 13% to 53% as shown in Table 12.5. The risk of pre-eclampsia in a subsequent pregnancy ranged from 0% to 16%. The incidence of pre-eclampsia after a normotensive index pregnancy was 0.7%.

Table 12.5 Summary of studies that presented the risk of recurrence of pregnancy-related hypertension in women with previous pre-eclampsia

Study	No. of participants	Recurrence % (*n*)	
		Gestational hypertension	Pre-eclampsia
Hjartardottir *et al.* (2006), Iceland[223]	151	34% (51)	13% (20)
Brown *et al.* (2007), Australia[224]	239	13% (31)	9% (22)
Hargood *et al.* (1991), Australia[226]	19	53% (10)	5% (1)
Hernandez-Diaz *et al.* (2009), Sweden[14]	19 540	–	14.7% (2871)
Trogstad *et al.* (2004), Norway[229] (singleton)	19 960	–	14% (2749)
Trogstad *et al.* (2004), Norway[229] (twin)	325	–	7% (23)
Campbell *et al.* (1985), Scotland[225]	279	30% (84)	7.5% (21)
Basso *et al.* (2001), Denmark[228]	8401	–	16% (1344)
Mostello *et al.* (2008), USA[230]	6157	–	15% (924)
Zhang *et al.* (2001), USA[227]	34	32% (11)	0% (0)

One large Swedish retrospective cohort study[14] [EL = 2+] investigated the risk of pre-eclampsia in pregnant women, including the risks of recurrence in second, third and fourth pregnancies. Out of 763 795 women studied, 31 417 had pre-eclampsia, giving an incidence risk of 3.0%. The risk was 4.1% in the first pregnancy and 1.7% in a later pregnancy; 19 540 of those who had had pre-eclampsia in their first pregnancy had a second pregnancy. The risk of recurrence of pre-eclampsia in the second pregnancy was 14.7% for women who had developed pre-eclampsia in their first pregnancy and 1.1% for those who had not. During the third pregnancy, the risk was 31.9% for women who had developed pre-eclampsia in the previous two pregnancies and remained 1.1% for those without a history of pre-eclampsia. For women with a first occurrence of pre-eclampsia in their second pregnancy, the risk was 15.9% during the third pregnancy, and 29.0% during the fourth pregnancy when they had developed pre-eclampsia in the previous two pregnancies. The risk of recurrence remained elevated (8.7%) in a third pregnancy where the second pregnancy was normotensive. For women with a first occurrence of pre-eclampsia in their third pregnancy, the risk was 14.7% during the fourth pregnancy. Among women without pre-eclampsia in their first pregnancy, the risk of pre-eclampsia was

0.83% if they became pregnant again within 2 years and 2.2% if they became pregnant more than 8 years after their first pregnancy; the corresponding risks were 13.1% and 15.8% for women with pre-eclampsia in their first pregnancy.

Effect of severity

Previous pregnancy with severe pre-eclampsia

One retrospective cohort study was conducted in the USA and investigated the recurrence of hypertensive disorders of pregnancy in 108 women with severe pre-eclampsia in the index pregnancy (gestational age 18–27 weeks).[231] [EL = 2+] These women had 169 subsequent pregnancies (follow-up: mean 5.4 years; range 2–12 years). The study showed that 65% (110 of 169) of subsequent pregnancies were complicated with pre-eclampsia, as shown in Table 12.6.

Two retrospective cohort studies used birth before 34 weeks of gestation as a surrogate for severe disease.[14 232] The first was a large Swedish retrospective cohort study that investigated the recurrence risk of pre-eclampsia.[14] [EL = 2+] Among women who had developed severe pre-eclampsia in their first pregnancy (defined as birth before 34 weeks for pre-eclampsia), the risk of any pre-eclampsia was 29% in their second pregnancy, and the risk of severe pre-eclampsia was 62 times higher (6.8%) than in women without pre-eclampsia in their first pregnancy (0.11%). During the third pregnancy, the risk of severe pre-eclampsia was 12.5% for women who had developed pre-eclampsia in the previous two pregnancies.

The second retrospective cohort study was conducted in the Netherlands and investigated the risk of recurrence of pre-eclampsia in subsequent pregnancy after early-onset pre-eclampsia (before 34 weeks) in the first pregnancy.[232] [EL = 2+] One hundred and twenty primiparous women were included (follow-up: mean 6.3 years). Twenty-seven women (22.5%) developed gestational hypertension in the next pregnancy while 30 others (25%) developed pre-eclampsia, as shown in Table 12.6.

The risk of recurrence of pre-eclampsia across the three cohort studies[14;231;232] ranged from 25% to 65%, as shown in Table 12.6. Recurrence of gestational hypertension in subsequent pregnancies was reported in only one of the studies (22.5%).

Women with previous HELLP syndrome

Three retrospective cohort studies[233-235] [EL = 2+] investigated the risk of recurrence of hypertensive disorders of pregnancy in subsequent pregnancies in women who had had HELLP syndrome in their index pregnancy. All studies were conducted in the USA and 435 women were included overall.

The risk of recurrence of HELLP syndrome in subsequent pregnancies ranged from 3% to 19%, as shown in Table 12.6 Recurrence of pre-eclampsia in subsequent pregnancies ranged from 24% to 55%; the largest recurrence risk (55%) was reported in a study in which delivery had occurred before 28 weeks.[235] One study reported results on developing gestational hypertension in subsequent pregnancies and showed a risk of 9% (19 of 212).

Previous pregnancy with eclampsia

Two cohort studies[236;237] [EL = 2+] investigated the risk of recurrence of hypertensive disorders of pregnancy in subsequent pregnancies in women who had had eclampsia in their index pregnancy.

The first study was a prospective cohort conducted in Nigeria that included 64 women who had had eclampsia during their index pregnancy.[236] [EL = 2+] These women were followed up in their next pregnancy. Ten women (16%) had a recurrence of eclampsia in next pregnancy, as shown in Table 12.6.

The second study was a retrospective cohort study conducted in the USA that included 182 women who had had eclampsia in their index pregnancy.[237] [EL = 2+] These women had 366 subsequent pregnancies (follow up: mean 7.2 years; range 3–13 years). One hundred and fifty-nine of these women were nulliparous (334 subsequent pregnancies) and 23 women were multiparous (32 subsequent pregnancies). The risk of recurrence of eclampsia in a subsequent pregnancy was 2% (seven of 366), while the risk of pre-eclampsia was 22% (80 of 366), as shown in Table 12.6.

Table 12.6 Summary of studies that presented the risk of recurrence of pregnancy-related hypertension in women with previous HELLP syndrome, eclampsia, severe pre-eclampsia or pre-eclampsia that had developed before 34 weeks of gestation

Index pregnancy	Study	No. of participants	Recurrence % (*n*)			
			Gestational hypertension	Pre-eclampsia	Eclampsia	HELLP syndrome
HELLP syndrome	Sullivan *et al.* (1994), USA[233]	161	–	43% (69)	–	19% (31)
	Sibai *et al.* (1995), USA[234]	212	9% (19)	24% (51)	–	3% (6)
	Chames *et al.* (2003), USA[235] (delivery before 28 weeks)	62	–	55% (34)	–	6% (4)
Eclampsia	Adelusi *et al.* (1986), Nigeria[236]	64	–	–	16% (10)	–
	Sibai *et al.* (1992), USA[237]	366	–	22% (80)	2%(7)	–
Severe pre-eclampsia	Sibai *et al.* (1991), USA[231] (severe pre-eclampsia)	169	–	65% (110)	–	–
	van Rijn *et al.* (2006), Netherlands[232] (delivery after 34 weeks)	120	22.5% (27)	25% (30)	–	–
	Hernandez-Diaz *et al.* (2009), Sweden[14] (delivery before 34 weeks)	1754	–	29% (509)	–	–

HELLP = haemolysis, elevated liver enzymes and low platelet count

Effect of gestational age at presentation

Previous pregnancy with gestational hypertension

A retrospective cohort study[223] [EL = 2+] was conducted in Iceland that investigated the risk of recurrence of hypertensive disorders of pregnancies in second pregnancies in 411 women who had had gestational hypertension in their first pregnancy. In comparison with late-onset gestational hypertension, early-onset gestational hypertension (34 weeks or earlier) was not associated with an increased risk of either gestational hypertension (OR 0.99; 95% CI 0.70 to 1.41) or pre-eclampsia (OR 0.58; 95% CI 0.25 to 1.35).

Another retrospective cohort study[225] [EL = 2+] was conducted in Scotland and investigated the risk of recurrence of hypertensive disorders of pregnancy in the second pregnancy in 1270 women who had had gestational hypertension in their first pregnancy. Comparison of women by gestational age at which they developed gestational hypertension in the index pregnancy showed that the risk of pre-eclampsia in the second pregnancy increased from 0% (none of 28) to 2.1% (26 of 1242) if the first pregnancy went to term (28–36 weeks versus 37–45 weeks). It also showed an increase in risk of gestational hypertension from 21% (six of 28) to 29.1% (361 of 1242).

Previous pregnancy with pre-eclampsia

A retrospective cohort study[225] [EL = 2+] conducted in Scotland investigated the risk of recurrence of hypertensive disorders of pregnancy in the second pregnancy in 264 women who had had pre-eclampsia in their first pregnancy. Comparison of women by the gestational age at which they had developed gestational hypertension in the index pregnancy showed that the risk of pre-eclampsia in the second pregnancy reduced from 13% (3 of 23) to 6.8% (16 of 234) if the first pregnancy went to term (28–36 weeks versus 37–45 weeks), and the risk of gestational hypertension reduced from 39.1% (nine of 23) to 29.5% (69 of 234)

A retrospective cohort study[230] [EL = 2+] conducted in the USA investigated recurrence of pre-eclampsia in the second pregnancy based on gestational age at delivery for the first pregnancy complicated by pre-eclampsia. The study included 6157 women who had had pre-eclampsia in their first pregnancy. The risk of recurrent pre-eclampsia was about 12% for those who had previously delivered at term and increased to nearly 40% for those whose prior delivery had occurred before 28 weeks.

A retrospective cohort study[223] [EL = 2+] conducted in Iceland also investigated the risk of recurrence of hypertensive disorders of pregnancies in the second pregnancy in 151 women

who had had pre-eclampsia in their first pregnancy. In comparison with late-onset pre-eclampsia, early-onset pre-eclampsia (34 weeks or earlier) was not associated with an increased risk of either gestational hypertension (OR 1.66; 95% CI 0.86 to 3.20) or pre-eclampsia (OR 1.33; 95% CI 0.47 to 3.77).

Previous pregnancy with HELLP syndrome

A retrospective cohort study[233] [EL = 2+] conducted in the USA investigated recurrence in subsequent pregnancies in women who had had HELLP syndrome in the index pregnancy (n = 121 women, 195 subsequent pregnancies).

The relationship of gestational age in primary and subsequent HELLP gestations was analysed relative to the 32-week gestation. Eighteen of the 36 women with recurrent HELLP pregnancies were originally delivered at 32 weeks or earlier. Eleven of these 18 (61%) were subsequently delivered at 32 weeks or earlier. Conversely, of the 18 women who were originally delivered after 32 weeks, only two (6%) were subsequently delivered before 32 weeks.

Previous pregnancy with eclampsia

A retrospective cohort study[237] [EL = 2+] conducted in the USA compared outcome in subsequent pregnancies in nulliparous women according to gestational age at the time of onset of eclampsia in the index pregnancy (159 nulliparous women, 334 subsequent pregnancies). The women who had had eclampsia before 37 weeks had statistically significantly higher incidences of pre-eclampsia in subsequent pregnancies as compared with women who had had eclampsia at 37 weeks or later (43% at 30 weeks or earlier; 32% at 31–36 weeks; 8% at 37–41 weeks; $P < 0.001$). For recurrence of eclampsia, no statistically significant differences were detected (30 weeks or earlier: 1.8%; 31–36 weeks: 1.7%; 37–41 weeks: 2.4%; P = NS).

Effect of severity and gestational age at presentation combined

The risk of recurrence of pre-eclampsia across the eight studies that investigated recurrence following a pregnancy complicated by severe pre-eclampsia, HELLP syndrome or eclampsia, or where any of these conditions had presented before 34 weeks,[14;233-235;237;237][47046}[232] ranged from 22% to 65%, as shown in Table 12.6.

Evidence statement

Gestational hypertension

In women with gestational hypertension in the index pregnancy, evidence from five retrospective cohort studies [EL = 2+] showed a recurrence risk for gestational hypertension of 16–47% and a recurrence risk for pre-eclampsia of 2–7%.

One retrospective cohort study [EL = 2+] (n = 411) showed no differences between late and early onset of gestational hypertension (34 weeks or earlier) in terms of risk of gestational hypertension or pre-eclampsia recurring in a subsequent pregnancy. Another retrospective cohort study, [EL = 2+] however, showed increases from 0% to 2.1% and from 21% to 29.1% in the risks of developing pre-eclampsia and gestational hypertension, respectively, in the second pregnancy if the first pregnancy went to term (28–36 weeks versus 37–45 weeks).

Pre-eclampsia

In women with pre-eclampsia in the index pregnancy, evidence from nine retrospective cohort studies [EL = 2+] showed a recurrence risk for gestational hypertension of 13–53% and a recurrence risk for pre-eclampsia of 0–16%.

The risk of recurrence of pre-eclampsia where the first occurrence of pre-eclampsia was not the first pregnancy was 15.9% in one large cohort study. [EL = 2+] The risk of recurrence remained elevated (8.7%) in a third pregnancy where the second pregnancy was normotensive.

In women with severe pre-eclampsia, a retrospective cohort study [EL = 2+] showed a 65% risk of developing pre-eclampsia in a subsequent pregnancy.

Two studies used birth before 34 weeks of gestation as a surrogate for severe disease. One large retrospective cohort study [EL = 2+] showed that, among women who had developed severe pre-eclampsia in their first pregnancy, the risk of any pre-eclampsia was 29% in their second pregnancy, and the risk of severe pre-eclampsia was 62 times higher (6.8%) than in women

without pre-eclampsia in their first pregnancy (0.11%). Another retrospective cohort study [EL = 2+] showed that there was a 22.5% risk of developing gestational hypertension and a 25% risk of developing pre-eclampsia in the next pregnancy.

Using HELLP syndrome as a surrogate for severity, evidence from three retrospective cohort studies [EL = 2+] reported recurrence risks of 3–19% for HELLP syndrome in a subsequent pregnancy, and 24–55% for pre-eclampsia. Only one of these studies reported a recurrence risk for gestational hypertension (9%).

Using eclampsia as a surrogate for severity, evidence from two cohort studies [EL = 2+] showed a risk of 2–16% for developing eclampsia in a subsequent pregnancy.

Examining the effect of gestational age at which the previous pre-eclampsia had developed, one retrospective cohort study [EL = 2+] ($n = 411$) showed no statistically significant differences between late and early onset of pre-eclampsia (34 weeks or earlier) in terms of recurrence risk for gestational hypertension or pre-eclampsia in a subsequent pregnancy. Another retrospective cohort study, [EL = 2+] however, showed that the risk of developing pre-eclampsia in the second pregnancy if the first pregnancy went to term (28–36 weeks versus 37–45 weeks) reduced from 13% to 6.8%, and the risk of developing gestational hypertension reduced from 39.1% to 29.5%. A large retrospective cohort study [EL = 2+] ($n = 6157$) showed that the recurrence risk of pre-eclampsia was about 12% for those who had previously delivered at term and increased to nearly 40% for those whose previous delivery had occurred before 28 weeks.

Another complex retrospective cohort study showed that women who had had eclampsia before 37 weeks had a statistically significantly higher incidence of pre-eclampsia in a subsequent pregnancy compared with women who had had eclampsia at 37 weeks or later (43% at 30 weeks or earlier; 32% at 31–36 weeks, 8% at 37–41 weeks; $P < 0.001$). No statistically significant difference was detected for recurrence of eclampsia.

GDG interpretation of the evidence

Gestational hypertension

There is evidence across different populations that the risk of recurrence of gestational hypertension in a woman who has had this condition in a previous pregnancy ranges from 16% to 47%; the risk of recurrence of pre-eclampsia ranges from 2% to 7%. The risks of gestational hypertension and pre-eclampsia when the first pregnancy was not complicated by gestational hypertension are 9% and 0.7%, respectively.

There are insufficient data to establish whether recurrence risk is dependent on the gestational age at presentation in the first pregnancy.

Pre-eclampsia

For pre-eclampsia, the evidence is more variable because definitions of the condition and methodologies differ between studies, but the risk of pre-eclampsia in a subsequent pregnancy ranges from 0% to 16%. This risk is independent of which pregnancy is the first to be complicated by pre-eclampsia; one study reported a recurrence risk of 8.7% in the third pregnancy even when the second pregnancy had been normotensive.

The risk of gestational hypertension in a subsequent pregnancy for a woman who has previously had pre-eclampsia ranges from 13% to 53%.

There is evidence that the risk of recurrent pre-eclampsia is increased (range 22–65%) where the index pregnancy had been complicated by severe disease (variously defined) or where disease of any severity had presented before 34 weeks. The GDG's view is that the recurrence risk of pre-eclampsia when birth occurs before 34 weeks in the index pregnancy is towards the lower end of this range (at about 25%, as reported in one of the included studies), and closer to the upper end of the range (at about 55%, as reported in another study) where birth had occurred before 28–30 weeks.

Recommendations

Tell women who had gestational hypertension that their risk of developing:

- gestational hypertension in a future pregnancy ranges from about 1 in 6 (16%) pregnancies to about 1 in 2 (47%) pregnancies
- pre-eclampsia in a future pregnancy ranges from 1 in 50 (2%) to about 1 in 14 (7%) pregnancies.

Tell women who had pre-eclampsia that their risk of developing:

- gestational hypertension in a future pregnancy ranges from about 1 in 8 (13%) pregnancies to about 1 in 2 (53%) pregnancies
- pre-eclampsia in a future pregnancy is up to about 1 in 6 (16%) pregnancies
- pre-eclampsia in a future pregnancy is about 1 in 4 (25%) pregnancies if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and about 1 in 2 (55%) pregnancies if it led to birth before 28 weeks.

12.6 Interpregnancy interval and recurrence of hypertensive disorders of pregnancy

Clinical effectiveness

A cohort study undertaken in Denmark between 1980 and 1994 to assess the risk or recurrent pre-eclampsia in relation to interpregnancy intervals and change of partner was identified.[228] [EL = 2+] There were 8401 women with a diagnosis of pre-eclampsia in their first pregnancy who had a subsequent pregnancy, and 26 596 with no pre-eclampsia in their first pregnancy. The risk of pre-eclampsia was estimated within each cohort according to whether the partner had changed. Interpregnancy interval was calculated from the birthday of the first child to the conception of the second. The results suggested no effect of change of partner on the risk of pre-eclampsia in the subsequent pregnancy. Women who had had pre-eclampsia in their first pregnancy did not seem to increase their risk with increased interpregnancy intervals but those who had not had pre-eclampsia in their first pregnancy had increasing risk with increased interpregnancy interval. The least risk in both groups was with an interpregnancy interval of less than 3 years. Maternal age, smoking history and social status were all confounders.

Evidence statement

One cohort study [EL = 2+] showed no effect of change of partner on the risk of pre-eclampsia in the subsequent pregnancy. Women who had had pre-eclampsia in their first pregnancy did not seem to increase their risk with increased interpregnancy intervals.

GDG interpretation of the evidence

There is no evidence for women whose pregnancy has been complicated by pre-eclampsia that delaying subsequent pregnancies for up to 10 years or changing partners increases the risk of recurrence.

Recommendation

Tell women who have had pre-eclampsia that there is no additional risk of recurrence with interpregnancy interval up to 10 years.

12.7 Body mass index and recurrence of hypertensive disorders of pregnancy

Clinical effectiveness

A retrospective cohort study conducted in the USA investigated recurrence of pre-eclampsia in the second pregnancy and investigated the effect of BMI of the women between the pregnancies.[230] [EL = 2+] The study included 6157 women who had had pre-eclampsia in their first pregnancy. The overall risk of recurrence in the second pregnancy was 14.7%.

The study showed pre-eclampsia risks increasing linearly with increasing BMI for all gestational age categories, as summarised in Table 12.7.

Table 12.7 Pre-eclampsia recurrence risk by current body mass index and gestational age of prior pre-eclampsia

Current BMI (kg/m²)	Recurrence risk by gestational age of prior pre-eclampsia		
	20–32 weeks	33–36 weeks	37–47 weeks
< 18.5	23.1%	14.3%	7.7%
18.5–24.9	29.3%	17.2%	9.5%
25–29.9	30.6%	25.3%	12.4%
30–34.9	32.4%	25.0%	17.5%
≥35.0	40.0%	29.1%	17.8%
Total	14.7%		

Evidence statement

One cohort study [EL = 2+] showed that the risk of recurrence of pre-eclampsia in women who had it in their first pregnancy increases linearly with increasing BMI.

GDG interpretation of the evidence

All women are advised to optimise general health prior to any pregnancy and that advice applies to women who have had hypertensive disorders during pregnancy.

BMI appears to be an independent variable for the development of recurrent pre-eclampsia, with a near-linear relationship irrespective of gestational age at presentation in the first pregnancy. The GDG feels that it is likely that achieving a BMI within the healthy range (18.5–24.9 kg/m², as per 'Obesity', NICE clinical guideline 43)[2] will reduce the recurrence risk and it is a modifiable factor.

Recommendation

Advise women who have had pre-eclampsia to achieve and keep a BMI within the healthy range before their next pregnancy (18.5–24.9 kg/m², 'Obesity', NICE clinical guideline 43).

13 References, abbreviations and glossary

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13.2 Abbreviations

ACE	angiotensin-converting enzyme
ACOG	American College of Obstetricians and Gynecologists
ALT	alanine aminotansferase
ANC	antenatal care
APCR	activated protein C resistance
ARB	angiotensin receptor blocker
ARDS	adult respiratory distress syndrome
AST	aspartate aminotransferase
ASTECS	the Antenatal Steroid for Term Elective Caesarean Section
b.i.d.	twice daily
BMI	body mass index
BPD	bronchopulmonary dysplasia
BPP	biophysical profile
CH	chronic hypertension
CHIPS	Control of Hypertension in Pregnancy Study
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CS	caesarean section
CTG	cardiotocography
dl	decilitre
EL	evidence level
FDA	Food and Drug Administration
g	gram
GA	gestational age
GDG	Guideline Development Group
GNI	gross national income
GP	general practitioner
GRIT	Growth Restriction Intervention Trial
HDU	high-dependency unit
HDZ	hydralazine
HES	hydroxy-ethylstarch
Hg	mercury
HTA	Health Technology Assessment
HYPITAT	Hypertension and Pre-eclampsia Intervention Trial
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IQR	interquartile range
IU	international unit
IUGR	intrauterine growth restriction
IVF	*in vitro* fertilisation
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
LR	likelihood ratio
MHRA	Medicines and Healthcare products Regulatory Agency

MD	mean difference
MDI	Mental Development Index
$MgSO_4$	Magnesium sulphate
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NEC	necrotising enterocolitis
NHS	National Health Service
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Health and Clinical Excellence
NICU	neonatal intensive care unit
NPV	negative predictive value
OR	odds ratio
PCWP	pulmonary capillary wedge pressure
PDI	Psychomotor Development Index
PPV	positive predictive value
QUADAS	quality assessment of studies of diagnostic accuracy in systematic review
QALY	quality-adjusted life year
RCT	randomised controlled trial
RI	resistance index
ROC	receiver operating characteristic
RPE	rating of perceived exertion
RR	relative risk
SCBU	special care baby unit
SD	standard deviation
SGA	small for gestational age
SLE	systemic lupus erythematosus
SPC	summary of product characteristics
UK	United Kingdom
USA	United States of America
WMD	weighted mean difference

13.3 Glossary

Absent end-diastolic velocities	Found during Doppler evaluation of umbilical artery and implying placental disease
ACE inhibitors	Angiotensin-converting enzyme inhibitors – an antihypertensive
Acetylsalicylic acid	Aspirin
Alanine aminotansferase (ALT)	A liver enzyme raised in presence of liver damage
Amniotic Fluid Index (AFI)	A method of amniotic fluid measurement by adding the biggest pools in each of the 4 quarters of the uterus
Albuminuria	Albumin is a type of protein in the blood which appears in urine in the presence of renal damage
Antenatal day unit	A unit established to undertake a variety of pregnancy assessments and so reduce the need for admission to hospital
Anticardiolipins	Antibodies which are formed against the cellular component cardiolipin
Antioxidants	Vitamins C and E are regarded as potent anti-oxidants
Antiphospholipid syndrome	Condition where have anticardiolipin antibodies and history of blood clots, miscarriage or poor pregnancy outcomes
Antiplatelet agents	Drugs that change the way platelets work
Antithrombin deficiency	One of the thrombophilias (see later), and one of the most severe types
Apgar scores	A way of assessing the baby at or shortly after birth by looking at heart rate, breathing, colour, muscle tone, reaction. It is marked out of 10
ARBs	Angiotensin receptor blocking agents – antihypertensives
Atenolol	A beta-blocker antihypertensive
Autoimmune disease	A disease in which the body raises antibodies against itself
Automated urinalysis	A method of testing for protein in the urine using an automated reagent-strip reading device
Beta-blocker	See atenolol
Bilirubin	Excretion product from the liver – in excess leads to jaundice
Biophysical profile (BPP)	A method of fetal assessment which includes fetal movement, fetal breathing fetal muscle tone, amniotic fluid volume and fetal cardiotocography
Body mass index	Measure of body build estimated from the individuals height and weight
Bupivacaine	A local anaesthetic used in regional anaesthesia
Calcium-channel blockers	Types of antihypertensives
Cardiotocograph (CTG)	A continuous recording of the fetal heart rate
Chronic hypertension	Hypertension that already exists – it can be primary (no obvious cause) or secondary to an underlying condition, such as renal disease
Clean catch specimen	A method of collecting urine to reduce contamination
Clonus	A muscle condition associated with hyper-reflexia and found in severe pre-eclampsia
Coagulation	Concerned with blood clotting
Coagulopathy	Where the blood clotting is abnormal; blood does not clot as well
Co-morbidities	Situation in which a number of different conditions co-exist
Congenital malformation	An abnormality of the baby present at birth
Converting enzyme DD	A rare genetic disorder associated with absent converting enzyme and increased tendency to thrombosis
Convulsions	Fits, seizures
Corticosteroids	Hormones produced by the adrenal gland and used to help mature a baby's lungs

Creatinine	Chemical excreted from the kidney that is used to assess how the kidney is working.
Crystalloid	A water soluble substance, i.e. salt
Dalteparin	A type of anticoagulant injection used to prevent blood clots
Day care evaluation	See antenatal care unit
Decelerations	Slowing of the fetal heart rate
Dinoprostone	A prostaglandin
Dipyridamole	An antiplatelet agent
Dipstick	An impregnated stick for testing urine
Diuretics	Drugs which encourage the kidneys to make urine, sometimes called 'water tablets'
Doppler velocimetry	A method of assessing both uterine and umbilical blood velocities, which helps work out if placenta working well
Ductus Arteriosus	The blood vessel located between the pulmonary artery and the aorta which is open in fetal life but which closes soon after birth
Eclampsia/eclamptic	A convulsive condition associated with pre-eclampsia
Egger test	A statistical test to see if there is bias in results
Electrolytes	Constituents of the blood which include sodium, potassium and chloride
Embryo-fetal adverse outcome	Loss or damage of either an embryo (usually as miscarriage) or as a fetus (usually as stillbirth, abnormality or growth restriction)
Enalapril	ACE inhibitor – a blood pressure lowering drug
Ephedrine	Adrenaline
Epidural	A method of pain relief involving placing a plastic tube in the back and giving drugs through it to stop pain
Epigastric pain	Pain in the upper central part of the abdomen
Esmolol	Beta-blocker antihypertensive
Established pre-eclampsia	Definite pre-eclampsia
Factor V Leiden	See thrombophilias
Factor II 20210A variant	Ditto
Fetal Biometry	Measurement of the fetus by ultrasound usually to include head, abdomen and femur length
Fetal growth restriction/IUGR	A condition in which the fetus fails to meet its growth potential; a small baby who is not growing
Fentanyl	A morphine-based drug for pain relief
Focal neurological deficit	Clinical evidence of localised nerve damage usually involving the brain
Fetal distress	A condition of the fetus usually arising from a lack in oxygen, and identified by the presence of an abnormal CTG
Foley catheter	A type of bladder catheter
Full blood count	Usually haemoglobin which measures degree of anaemia, white cell count indicating infection and platelet count which is involved in clotting
FVL homozygous	See thrombophilias
Genotype/specific genotype	The genetic makeup of an individual
Gestational hypertension	New hypertension that starts after 20 weeks of pregnancy and where there is no proteinuria
Haemoglobin	Found in red blood cells it carries oxygen. Measures anaemia
Haematuria	Blood in the urine
Haematological evaluation	Tests of the blood
Haemodynamic response	Term used to describe the heart and blood vessel response usually to treatment

Haemolysis	Breakdown of red blood cells
HELLP syndrome	Haemolysis, elevated liver enzymes and low platelet count; a type of severe pre-eclampsia
Heterozygous	State of different genes at the same locus on the chromosome
Hydralazine	A smooth muscle relaxant antihypertensive usually only used where severely high blood pressure
Hyperbilirubinaemia	Excessive bilirubin in the blood
Hyperglycaemic	Excessive glucose in the blood
Hyperhomocysteinaemia	See thrombophilias
Hyperkalaemia	Excessive potassium in the blood
Hyperlipidaemia	Excessive lipids in the blood
Hyperreflexia	Increased reflexes for example knee jerk
Hypertension	High blood pressure
Hypertension (mild, moderate, severe)	See introduction for definitions used
Hypotension	Low blood pressure
Infusion pump	A pump used to help fluids into a patient usually via a vein
Intracranial pressure	Pressure within the skull
Intubation	Technique whereby a tube is placed in the patient windpipe to aid breathing or for anaesthetic purposes
Ischaemic heart disease	Usually term used to describe coronary heart disease (heart attack or angina)
Labetalol	A blood pressure treatment that has beta- and alpha-blocker actions
Lactic dehydrogenase	Enzyme released by tissue damage
Linoleic acid	Type of fatty acid
Low birthweight	A term used to define babies weighing less than 2.5 kg
Lupus anticoagulants	Type of auto-antibodies that increase the risk of blood clots
Lytic cocktail	A mixture of pethidine, chlorpromazine and promethazine used to prevent fits in pre-eclampsia/eclampsia
Mechanical ventilation	Assisted ventilation
Meriperidine	Opioid drug for pain relief. Better known as Demerol
Methyldopa	Centrally acting drug that lowers blood pressure
Microalbumin	Very small amounts of the protein albumin in the urine. It is used as a test of kidney function.
Multi-gravid	More than 1 pregnancy
Multiparous	More than 1 pregnancy resulting in a stillbirth after 24 weeks or a live birth
Multiple pregnancy	Pregnancy with more than one fetus
MTHFR homozygous	See thrombophilia
Naloxone	A drug which reverses the respiratory depressant effects of morphine-based drugs
Neonate	A baby between 7 and 28 days of life
Nitric oxide agents/donors/precursors	Drugs that cause blood vessels to dilate
Non-reassuring fetal heart rate	A classification of the fetal heart rate that means possible fetal distress. It can sometimes mean abnormal.
Normotensive	Normal blood pressure
Nulliparous/nulliparity	First pregnancy
Obesity	Overweight defined by BMI or by weight
Oedema	Waterlogging of the tissue; swelling

Offer birth	Offer elective early birth through induction of labour or by elective caesarean section if indicated
Oligohydramnios	Reduced amounts of amniotic fluid around the fetus
Oliguria	Reduced urine production. Can be defined as about 500 ml per day or < 20 ml per hour for 2 consecutive hours.
Opioid	Morphine-based drugs
Oxytocin augmentation	Use of the drug oxytocin to stimulate labour that has already started
Palpitations	Irregular heart beat felt by the patient as flutters
Parenteral	Route of administration – usually via the vein or muscle
Patent Ductus Ateriosus	See ductus arteriosus
Perinatal	Usually defined as a period from 24 weeks' gestation to 7 days after birth
pH scale	A logarithmic scale used to assess acidity
Placental abruption	Separation of the placenta before the baby is born
Plasma	The fluid, non-cellular part of the blood
Platelets	Small cellular fragments responsible for blood clotting
Ponderal index	An index of fat content usually in babies
Positive roll-over test	An archaic test of risk of pre-eclampsia
Postpartum haemorrhage	Blood loss from the genital tract after birth of > 500 mls
Pre-eclampsia	New hypertension after 20 weeks of pregnancy with significant proteinuria (more than 300 mg in a 24-hour urine collection or more than 30mg/mmol in a spot urinary protein : creatinine ratio sample)
Prematurity	Relates to a fetus/baby born before 37 weeks' gestation
Preterm birth/delivery	A birth occurring before 37 weeks' gestation
Pregnancy-induced hypertension	See gestational hypertension. The term is sometimes used to mean both gestational hypertension and pre-eclampsia
Primiparous/primiparity/primigravida	First pregnancy
Prognosis	Likely eventual outcome
Promethazine	Antihistamine type drug used for sedation/antiemetic
Protein C deficiency	See thrombophilia
Protein S deficiency	See thrombophilia
Proteinuria	Protein in the urine – see albuminuria
Prothrombin	A protein associated with blood clotting
Pulmonary oedema	
Respiratory distress syndrome	A condition of the newborn when the lungs are immature because they are not producing enough of a substance called surfactant
Retrolental fibroplasia	An eye condition associated with prematurity
Secondary care setting	Hospital based care
Seizure	Fit
Serum	Fluid which exudes from clotted plasma
Severe hypertension	Diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160 mmHg or greater.
Severe pre-eclampsia	Severe pre-eclampsia is pre-eclampsia with severe hypertension and/or with symptoms, and/or biochemical and/or haematological impairment.
Single Deepest Vertical Pool (SVDP)	A measure of amniotic fluid where the largest individual pool of fluid in recorded
Significant proteinuria	> 300 mg/24 hours in a 24-hour urine collection or >30mg/mmol in a spot urinary protein : creatinine ratio sample
Systemic lupus erythematosis	A chronic inflammatory condition that can involve joints, kidneys, heart lungs and brain.

Small for gestational age	Usually defined as being below a certain birthweight for weeks of pregnancy. Can be written as less than 5th or 10th.
Spontaneous vaginal birth	Birth unaided by instruments
Spot protein: creatinine ratio	A one off test for urine protein excretion
Stillbirth	A baby born dead after 24 weeks gestation
Thrombocytopaenia	A reduced number of platelets in the blood
Thromboembolism	A blood clot in the circulation
Thrombophilia	The thrombophilias are a family of conditions , some genetic others acquired which are associated with an increased chance for the individual to form clots in their circulation
Tramadol	A morphine-like analgesic
Transaminases	Liver enzymes which are elevated when there is cellular damage in the liver
Umbilical artery Doppler scan	A technique to estimate blood velocity in the umbilical artery
Uric acid	A blood analyte which can be increased if the kidneys are not working well enough
Visual scotomata	A condition in which there are blind areas within the individual's visual fields
Xylocaine	Local anaesthetic

Health economics terms

Cost–consequence analysis	A form of economic evaluation where the costs and consequences of two or more interventions are compared, and the consequences are reported separately from costs.
Cost-effectiveness analysis	A form of economic evaluation in which consequences of different interventions are measured using a single outcome, usually in 'natural' units (for example, life-years gained, deaths avoided, heart attacks avoided, cases detected). Alternative interventions are then compared in terms of cost per unit of effectiveness.
Cost-minimisation analysis	A form of economic evaluation that compares the costs of alternative interventions that have equal effects.
'Cost of illness' study	A study that measures the economic burden of a disease or diseases and estimates the maximum amount that could potentially be saved or gained if a disease was eradicated.
Cost–utility analysis	A form of cost-effectiveness analysis in which the units of effectiveness are quality-adjusted life years (QALYs).
Decision(-analytic) model (and/or technique)	A model of how decisions are or should be made. This could be one of several models or techniques used to help people to make better decisions (for example, when considering the trade-off between costs, benefits and harms of diagnostic tests or interventions).
Decision tree	A method for helping people to make better decisions in situations of uncertainty. It illustrates the decision as a succession of possible actions and outcomes. It consists of the probabilities, costs and health consequences associated with each option. The overall effectiveness or cost effectiveness of different actions can then be compared.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominate (in cost-effectiveness analysis)	A term used in health economics when a treatment option is both more clinically effective and less costly than an alternative option. This treatment is said to 'dominate' the less effective and more costly option.

Economic evaluation	Comparative analysis of alternative health strategies (interventions or programmes) in terms of both their costs and their consequences.
Equity	Fair distribution of resources or benefits.
Health-related quality of life	A combination of a person's physical, mental and social wellbeing; not merely the absence of disease.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.
Markov modelling	A decision-analytic technique that characterises the prognosis of a cohort of patients by assigning them to a fixed number of health states and then models transitions among health states.
Model input	Information required for economic modelling. For clinical guidelines, this may include information about prognosis, adverse effects, quality of life, resource use or costs.
Net benefit estimate	An estimate of the amount of money remaining after all payments made are subtracted from all payments received. This is a source of information used in the economic evidence profile for a clinical guideline.
Opportunity cost	The opportunity cost of investing in a healthcare intervention is the other healthcare programmes that are displaced by its introduction. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Quality-adjusted life year (QALY)	An index of survival that is adjusted to account for the patient's quality of life during this time. QALYs have the advantage of incorporating changes in both quantity (longevity/mortality) and quality (morbidity, psychological, functional, social and other factors) of life. Used to measure benefits in cost–utility analysis.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations.
One-way sensitivity analysis (univariate analysis):	Each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.
Probabilistic sensitivity analysis:	Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).

Appendix A

Scope of the guideline

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Hypertension in pregnancy: the management of hypertensive disorders during pregnancy

1.1 Short title

Hypertensive disorders during pregnancy

2 Background

a) The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Women's and Children's Health to develop a clinical guideline on hypertension in pregnancy for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health (see appendix). The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

b) The Institute's clinical guidelines support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework has been published. The statements in each NSF reflect the evidence that was used at the time the Framework was prepared. The clinical guidelines and technology appraisals published by the Institute after an NSF has been issued have the effect of updating the Framework.

c) NICE clinical guidelines support the role of healthcare professionals in providing care in partnership with patients, taking account of their individual needs and preferences, and ensuring that patients (and their carers and families, where appropriate) can make informed decisions about their care and treatment.

3 Clinical need for the guideline

a) Successive confidential enquiries into maternal deaths have highlighted continuing problems with the management of severe peripartum hypertension. The numbers of women presenting both with risk factors for the development of hypertensive disease during pregnancy and with pre-existing hypertensive disease are increasing.

b) Other national bodies have repeatedly addressed the management of severe pre-eclampsia once it presents. However, they have not covered care while planning pregnancy, during pregnancy before pre-eclampsia develops, or following a pregnancy during which hypertensive disease has occurred. There is wide variation in practice in these areas, with likely over investigation and treatment, including hospital admission. There is little professional guidance for primary care physicians caring for women who are either planning pregnancy or have completed pregnancy.

4 The guideline

a) The guideline development process is described in detail in two publications that are available from the NICE website (see 'Further information'). 'The guideline development process: an overview for stakeholders, the public and the NHS' describes how organisations can become involved in the development of a guideline. 'The guidelines manual' provides advice on the technical aspects of guideline development.

b) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health (see appendix).

c) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

a) Women who present with hypertensive disorders for the first time during pregnancy.

b) Women who have pre-existing hypertension and are planning pregnancy or are pregnant.

c) Women who are pregnant and at increased risk of developing hypertensive disorders during pregnancy.

d) The fetus until birth.

4.1.2 Groups that will not be covered

a) Women with hypertension and diabetes (for care of these women, refer to 'Diabetes in pregnancy' NICE clinical guideline 63 [2008]).

b) The infants of women who have had hypertensive disorders during pregnancy.

4.2 Healthcare setting

a) Primary care, including community midwifery settings.

b) Secondary care, including obstetric and general medical services.

4.3 Clinical management

4.3.1 The guideline will cover

a) For the purposes of this guideline 'pregnancy' will include the antenatal, intrapartum and postpartum (6 weeks after birth) periods.

b) Information and advice for women who have existing hypertension and are pregnant or planning to become pregnant.

c) Information and advice for women who are pregnant and at increased risk of developing hypertensive disorders during pregnancy.

d) Assessment and management of women who present with hypertension without proteinuria during pregnancy (gestational hypertension).

e) Assessment of women who present with or develop hypertension and proteinuria during pregnancy (pre-eclampsia), and their management before admission critical care level 2 setting during the peripartum period.

f) Management of pre-eclampsia and its complications in a critical care setting.

g) Assessment and management of women with pre-existing hypertension during their pregnancy and the postnatal period.

h) Information, advice and support for women and healthcare professionals following discharge to primary care following a pregnancy complicated by hypertension.

i) Care of the fetus during a pregnancy complicated by hypertensive disorder.

j) The Guideline Development Group will consider making recommendations on the principal complementary and alternative interventions or approaches to care relevant to the guideline topic.

k) The Guideline Development Group will take reasonable steps to identify ineffective interventions and approaches to care. If robust and credible recommendations for re-positioning the intervention for optimal use, or changing the approach to care to make more efficient use of resources can be made, they will be clearly stated. If the resources released are substantial, consideration will be given to listing such recommendations in the 'Key priorities for implementation' section of the guideline.

4.3.2 The guideline will not cover

a) The detection of hypertension during pregnancy. This is covered in 'Antenatal care', NICE clinical guideline 62 (2008).

b) Screening strategies for risk factor identification.

4.4 Status

4.4.1 Scope

This is the final scope.

NICE has published the following related guidance:

- Diabetes in pregnancy: management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63 (2008)
- Antenatal care: routine care for the healthy pregnant woman (update) NICE clinical guideline 62 (2008)
- Intrapartum care: care of healthy women and their babies during childbirth. NICE clinical guideline 55 (2007)
- Routine postnatal care of women and their babies. NICE clinical guideline 37 (2006)
- Induction of labour. NICE inherited guideline D (2001).

NICE is in the process of developing the following related guidance:

- Labour: induction of labour (update of NICE inherited guideline D). NICE clinical guideline. Publication expected June 2008.

4.4.2 Guideline

The development of the guideline recommendations will begin in April 2008.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.

These are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

Appendix A: Referral from the Department of Health

The Department of Health asked NICE:

'To develop a clinical guideline on the management of hypertension in pregnancy.'

Appendix B

Declarations of interest

This appendix includes all interests declared on or before 9 August 2010.

GDG members

Chris Barry
No interests declared

Rachel Fielding
No interests declared

Pauline Green
No interests declared

Jane Hawdon
Personal non-pecuniary interests: Chair of Breastfeeding Manifesto Coalition

Surbhi Malhotra
No interests declared

Fiona Milne
Personal pecuniary interests: Consultant to Almere in relation to the development of point-of-care testing for placental growth factor as a potential marker for pre-eclampsia (no products currently available commercially)

Personal non-pecuniary interests: Coordinator of the Pre-eclampsia Community Guideline (PRECOG) GDG under the auspices of Action on Pre-eclampsia

Susan Mitchinson
No interests declared

Lynda Mulhair
No interests declared

Adam North
No interests declared

Derek Tuffnell
Personal non-pecuniary interests: Adviser to Baby Lifeline; research interests in hypertensive disorders during pregnancy (not commercially funded)

James Walker
Personal pecuniary interests: Chairman of Centre for Maternal and Child Enquiries (CEMACE); chairman of and shareholder in spin-out companies studying predictors of pre-eclampsia (not operating commercially at present); advisor to the National Patient Safety Agency (NPSA)
Personal non-pecuniary interests: member of the Board of Trustees of Action on Pre-eclampsia; International Society for the Study of Hypertension in Pregnancy

Stephen Walkinshaw
No interests declared

David Williams
No interests declared

NCC-WCH staff and contractors

M Qutayba Almerie
No interests declared

Khalid Ashfaq
No interests declared

Ella Fields
No interests declared

David James
No interests declared

Rajesh Khanna
No interests declared

Angela Kraut
No interests declared

Rosalind Lai
No interests declared

Moira Mugglestone
No interests declared

Leo Nherera
No interests declared

Debbie Pledge
No interests declared

Cristina Visintin
No interests declared

Martin Whittle
Personal pecuniary interests: Adviser to National Screening Committee in relation to obstetric ultrasound services

External advisers

Martin Dresner
No interests declared

Edmund Lamb
Non-personal pecuniary interests: Consultancy for Siemens (for point-of-care testing device for urinary albumin)
Personal non-pecuniary interests: GDG member for 'Chronic kidney disease' (NICE clinical guideline 73)[33] *and research interests in effectiveness of methods of measuring urinary protein*

Andrew Shennan
Personal pecuniary interests: Adviser to Roche Diagnostics (for prediction of pre-eclampsia
Non-personal pecuniary interests: Validation of blood pressure devices for A and D, GE Medical, Health and Life, Microlife, Nessei, Omron, Rossmax, Spengler; development of patent for markers of pre-eclampsia for Perkin-Elmer
Personal non-pecuniary interests: Adviser to Action on Pre-eclampsia; member of PRECOG GDG

Paul Stevens
Personal non-pecuniary interests: GDG member for 'Chronic kidney disease' (NICE clinical guideline 73)[33] *and research interests in effectiveness of methods of measuring urinary protein*

Appendix C

Registered stakeholder organisations

Action on Pre-Eclampsia
All About Nocturnal Enuresis Team
Association of the British Pharmaceuticals Industry,(ABPI)
AstraZeneca UK Ltd
Barnsley Hospital NHS Foundation Trust
Barnsley PCT
Bedfordshire PCT
Birmingham Women's Healthcare Trust
Birth Trauma Association
Blood Pressure Association
BMFMS
Bournemouth and Poole PCT
Bradford Teaching Hospitals NHS Foundation trust
Brighton and Sussex University Hospitals Trust
British Cardiovascular Society
British Hypertension Society
British National Formulary (BNF)
Cambridge University Hospitals NHS Foundation Trust
CIS'ters
Cochrane Pregnancy & Childbirth Group
Commission for Social Care Inspection
Connecting for Health
Conwy and Denbighshire NHS Trust
Cytyc UK Limited
Department of Health
Department of Health, Social Security and Public Safety of Northern Ireland
Derbyshire Mental Health Services NHS Trust
Dudley Group of Hospitals NHS Trust
East & North Herts PCT & West Herts PCT
Health Commission Wales
Healthcare Commission
Infermed Ltd
JBOL Ltd
Kingston Hospital NHS Trust
Kirklees Primary Care Trust
La Leche League GB
Leeds PCT
Leeds Teaching Hospitals NHS Trust
Liverpool Women's NHS Foundation Trust
Liverpool Women's NHS Trust
Luton & Dunstable Hospital NHS Foundation Trust
Medicines and Healthcare Products Regulatory Agency (MHRA)
Mid and West Regional Maternity Services Liaison Committee
National Childbirth Trust
National Patient Safety Agency (NPSA)
National Public Health Service - Wales
National Screening Committee
National Treatment Agency for Substance Misuse

NHS Direct
NHS Plus
NHS Purchasing & Supply Agency
NHS Quality Improvement Scotland
North Cheshire Hospitals
North Tees and Hartlepool Acute Trust
North Yorkshire and York PCT
Northern Lincolnshire and Goole Hospitals NHS Foundation Trust
Northumbria Healthcare NHS Foundation Trust
Obstetric Anaesthetists Association
P.M.S (Instruments) Ltd
Partnerships for Children, Families, Women and Maternity
PERIGON Healthcare Ltd
PRIMIS+
Programme development Group in Maternal and Child Nutrition
RCM Consultant Midwives Group
Roche Diagnostics
Royal Brompton & Harefield NHS Trust
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians of London
Royal College of Physicians of London
Royal Society of Medicine
SACAR
Salford Royal Hospitals Foundation NHS Trust
Sandwell & West Birmingham Hospitals NHS Trust
Sandwell PCT
Sanofi-Aventis
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Sherwood Forest Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Solvay Healthcare Limited
Southampton University Hospital Trust
Syner-Med Pharmaceutical Products Ltd
Takeda UK
Tameside Acute Trust
The British Dietetic Association
The British Renal Society
The Renal Association
UCLH NHS Foundation Trust
United Lincolnshire Hospitals NHS Trust
University College London Hospitals NHS Foundation Trust
University of Leicester (The Infant Mortality & Morbidity Studies)
Wellbeing of Women
Welsh Assembly Government
Welsh Scientific Advisory Committee
Wiltshire PCT
Wirral University Teaching Hospital NHS Foundation Trust
Worthing and Southlands Hospital
York Hospital NHS Foundation Trust
Yorkshire and the Humber LS

Appendix D

Clinical questions

- What interventions (including lifestyle advice) are effective at reducing the incidence of hypertensive disorders in pregnancy?
- What advice/interventions should be offered to women with chronic hypertension planning to become pregnant?
- What interventions for chronic hypertension are effective at improving outcomes for women and infants?
- What investigations, monitoring and advice should take place when gestational hypertension is diagnosed?
- What interventions are effective in improving outcomes for women and infants of women with gestational hypertension?
- What are the indications for timing, place and mode of birth in women with gestational hypertension?
- What advice, investigations and monitoring should take place when pre-eclampsia is diagnosed?
- What interventions are effective in improving outcomes for women and infants in women with pre-eclampsia?
- What are the indications for timing of birth in women with pre-eclampsia?
- What is the appropriate medical management of women with severe pre-eclampsia or its complications in a critical care situation?
- What is the appropriate obstetric care of women with hypertensive disorders in pregnancy in the intrapartum period?
- What investigations, monitoring and advice should be given to women with hypertensive disorders of pregnancy, especially for those who wish to breastfeed, following discharge from critical care level 2/3?
- How should women, who were hypertensive in pregnancy, especially for those who wish to breastfeed, be managed in the postnatal period?
- What fetal assessments should occur in chronic hypertension, gestational hypertension or pre-eclampsia?
- What advice should be given to women who have had hypertension in pregnancy at discharge from maternity care?

Appendices E–G

These appendices are presented in separate files.

Appendix H

Cost effectiveness of aspirin compared with no aspirin in preventing pre-eclampsia in women at risk of developing pre-eclampsia

Introduction

Pre-eclampsia is associated with high maternal and neonatal morbidity and mortality. Worldwide, pre-eclampsia and eclampsia are estimated to be responsible for approximately 14% of maternal deaths per year (50 000–75 000).[238] Pre-eclampsia is estimated to account for one-fifth of antenatal admissions, two-thirds of referrals to day-care assessment units and one-quarter of obstetric admissions to intensive care units in the UK.[239] Interventions that aim to reduce the risk of pre-eclampsia may be cost effective or even cost saving if the intervention leads to lower overall health service costs by reducing the need for continuing assessment and admission and thereby freeing up scarce NHS resources to be used to improve health in other ways.

An economic model was developed to consider the use of aspirin in the prevention of pre-eclampsia. The question was partially addressed by Meads *et al.* (2008).[39] However, the GDG considered that the reported test accuracy and effectiveness data in that study were not sufficiently robust to be used in this model since the data were obtained from heterogeneous populations. Instead, the economic model developed for this guideline used data from the PARIS study,[42] which showed that aspirin was clinically effective in preventing pre-eclampsia.

Objectives

To determine the cost effectiveness of aspirin versus usual management in the prevention of pre-eclampsia and its complications in women at risk of developing pre-eclampsia.

Model structure and assumptions

A probabilistic model was developed in Microsoft Excel™. The analytic structure is illustrated by the schematic in Figure H.1. In the model, all women have pregnancy-related hypertension at week 12 of their pregnancy and are at risk of developing pre-eclampsia. For simplicity, Figure H.1 shows only a sub-tree of the whole model representing those women who develop pre-eclampsia. The pathway is identical for women who do not develop pre-eclampsia. The model includes the following maternal outcomes: delivery before 34 weeks, delivery of babies who are small for gestational age (SGA), and death. Outcomes for the neonatal infant are: delivered healthy with no admission, delivered healthy and admitted, and delivered healthy but die before discharge.

Model event rates

The incidence of maternal outcomes were taken from the placebo arm of the PARIS study.[42] Neonatal admissions were taken from Habli *et al.* (2007).[145] The baseline data with no treatment and the treatment effectiveness data (both taken from the PARIS study[42]), are shown in Tables H.1 and H.2, respectively. The outcomes of interest were pre-eclampsia, perinatal and maternal deaths, SGA babies, birth before 34 weeks, hospitalisation, maternal and neonatal quality of life, and healthcare costs. The side effects of aspirin were not explicitly considered as

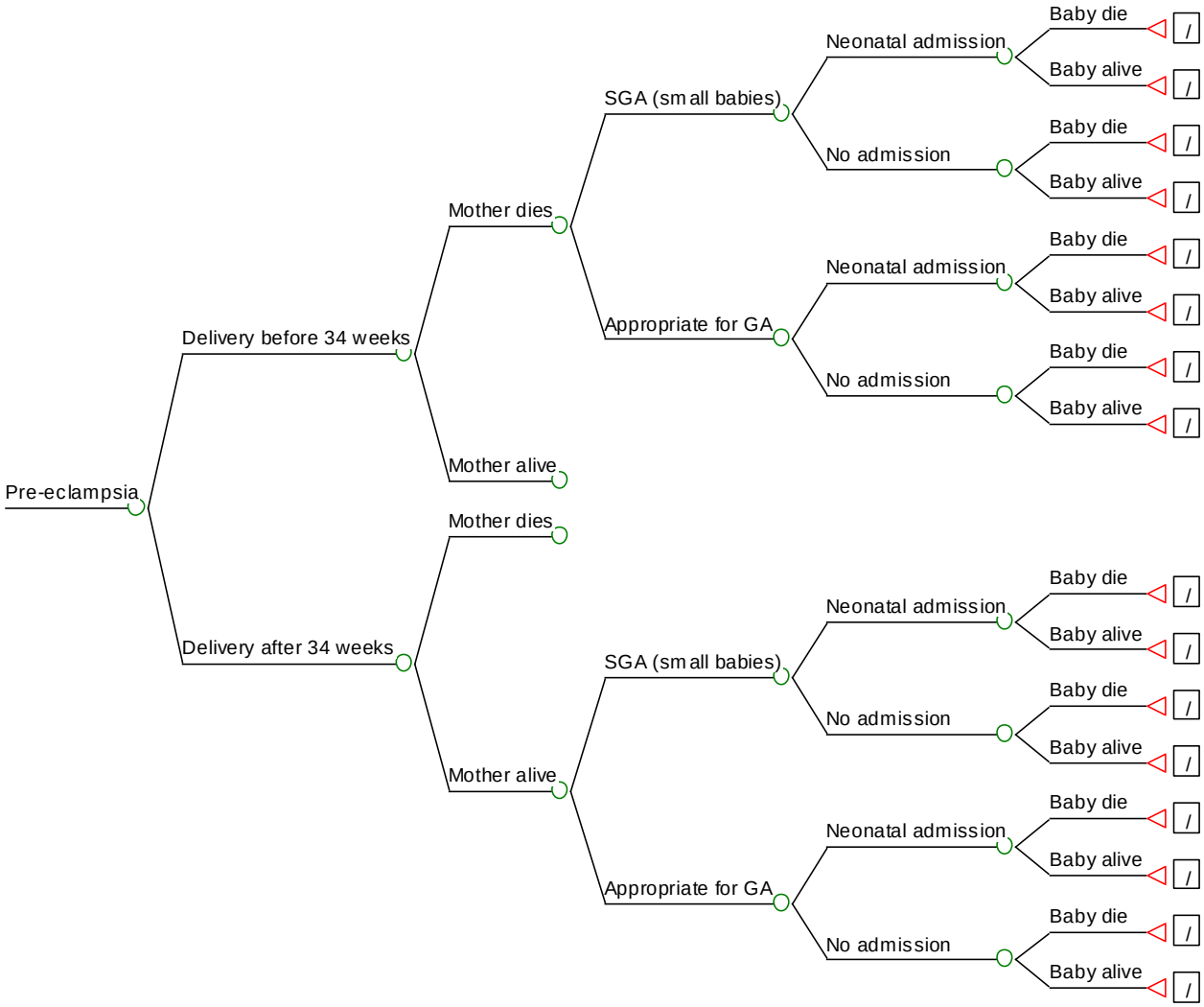

Figure H.1 Model structure for the cost effectiveness of aspirin in preventing pre-eclampsia (pre-eclampsia sub-tree shown)

the GDG felt that the aspirin dose recommended for use in this population is sufficiently small (75 mg) and treatment duration sufficiently short not to have any significant side effects such as internal bleeding.

Cost inputs

In accordance with NICE methods for clinical guidance,[38] a public sector, NHS and Personal Social Services (PSS) perspective was adopted.

A systematic review of the economic literature to search for costs was undertaken as part of the guideline development process. All costs are presented in GB pounds, at 2008–09 prices. Drug costs were taken from the *British National Formulary*[198] and the cost of other outcomes were taken from NHS reference costs.[240] The model's cost inputs are shown in Table H.3. It was assumed that women who did not develop pre-eclampsia gave birth in an obstetric unit and no assumptions were made about the mode of delivery since the GDG consensus was that aspirin had no impact on this. For simplification, it was assumed that each woman had an uncomplicated vaginal delivery.

Table H.1 Baseline event rates with no treatment: all women with pregnancy-related hypertension who are at risk of developing pre-eclampsia, and by gestational age

Outcome	Model value	Distribution	Alpha	Beta	Source
Pre-eclampsia	0.087	Beta	1340	14001	Askie *et al.*[42]
Delivery < 34 weeks	0.072	Beta	1111	14412	Askie *et al.*[42]
SGA	0.059	Beta	624	10030	Askie *et al.*[42]
Baby death before discharge	0.034	Beta	524	14736	Askie *et al.*[42]
Maternal death	0.000	Beta	23.24	1999977	Lewis[145]
Event rates after 34 weeks of gestation NO pre-eclampsia					
SGA	0.098	Beta	37	342	Habli *et al.*[145]
Admission to NICU	0.132	Beta	50	329	Habli *et al.*[145]
Neonatal death	0.004	Beta	4.1	995.9	CEMACH[241]
Event rates after 34 weeks of gestation with pre-eclampsia					
SGA	0.192	Beta	30	126	Habli *et al.*[145]
Admission to NICU	0.333	Beta	52	104	Habli *et al.*[145]
Neonatal death	0.004	Beta	4.2	995.8	CEMACH[241]
Event rates before 34 weeks of gestation NO pre-eclampsia					
SGA	0.211	Beta	20	75	GDG estimate
Admission to NICU	0.685	Beta	1327	611	Marret *et al.*[242]
Neonatal death	0.044	Beta	85	1866	Marret *et al.*[242]
Event rates before 34 weeks of gestation with pre-eclampsia					
SGA	0.211	Beta	20	75	Sibai *et al.*[145]
Admission to NICU	0.874	Beta	83	12	Sibai *et al.*[145]
Neonatal death	0.150	Beta	150	850	GDG estimate

NICU = neonatal intensive care unit; SGA = small for gestational age

Table H.2 Treatment effects of aspirin in all women with pregnancy-related hypertension who are at risk of developing pre-eclampsia

Outcome	Model value	Distribution	LN(mean)	Lower CI	Upper CI	Standard error	Source
Pre-eclampsia	0.90	Lognormal	−0.11	0.84	0.97	0.04	Askie *et al.*[42]
Delivery < 34 weeks	0.91	Lognormal	−0.09	0.83	0.98	0.04	Askie *et al.*[42]
Baby death before discharge	0.90	Lognormal	−0.11	0.81	1.03	0.06	Askie *et al.*[42]
SGA	0.90	Lognormal	−0.11	0.81	1.01	0.06	Askie *et al.*[42]
Any of the above	0.90	Lognormal	−0.11	0.85	0.96	0.03	Askie *et al.*[42]

SGA = small for gestational age

Table H.3 Health service costs incurred by women with pre-eclampsia, 2008–09

Outcome	Cost	Source
Pre-eclampsia	£9,000	Meads *et al.*[39]
Delivery > 34 weeks	£1,923	NHS Reference Costs[240]
Birth without complications at obstetric unit	£1,014	NHS Reference Costs[240]
SGA	£1,130	NHS Reference Costs[240]
Admissions	£713	NHS Reference Costs[240]
Liveborn baby alive	£634	NHS Reference Costs[240]
Cost of aspirin, over 26 weeks	£6.24[a]	*British National Formulary*[198]

SGA = small for gestational age

[a] It was assumed that women start taking aspirin at 12 weeks through to 38 weeks at the cost of £0.24 per week, i.e. taking 1 × 75 mg tablet per day

Valuing outcomes

The Harvard Cost-Effectiveness Registry was searched for quality of life values associated with normotensive pregnant women. One study was identified that evaluated the cost effectiveness of contraception methods in women of average health and fertility, ranging from 15 to 50 years of age compared with non-use of contraception.[243] The authors found that short-term loss of quality of life due to pregnancy was 0.0375.

For this guideline, no quality of life data associated with pre-eclampsia could be identified and therefore it was assumed that those who developed pre-eclampsia had the same quality of life as normotensive pregnant women, based on GDG opinion. It was assumed that all children discharged alive would live a normal healthy life up to 80 years and have 27.7 discounted quality-adjusted life years (QALYs). Thus the total QALYs lost was the sum of maternal and neonatal QALY loss. The model's QALY value are shown in Table H.4.

Table H.4 Quality of life loss assigned to pregnant women and neonatal death (QALYs)

Outcome	QALY loss	Source
Normotensive pregnant women	−0.0274[a]	Sonnenberg *et al.*[243]
Pre-eclampsia	−0.0274	Sonnenberg *et al.*[243]
Neonatal death	−27.7	Calculated, discounting life expectancy at 3.5%

[a] The QALY loss was derived from data taken from the study by Sonnenberg *et al.*[243] that found that the utility loss from pregnancy was 0.0375; to convert this utility loss to QALY loss, the utility loss was divided by 52 to get a weekly utility loss, and then multiplied by 38 for those who delivered at term and by 35 for those who delivered preterm

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to explore to what extent the results were affected by the uncertainty surrounding the model input parameters. In PSA, each model parameter is assigned a distribution reflecting the expected sampling variation. Costs and effects are determined after simultaneously selecting random values from each distribution. The process is repeated many times in a Monte Carlo simulation to give an indication of the extent to which model input parameter uncertainty affects the incremental cost-effectiveness ratio (ICER), that is, change the relative order of cost effectiveness between alternatives. Distributions were not applied to cost parameters as there was generally little uncertainty associated with this data, but treatment costs of pre-eclampsia were varied in one-way sensitivity analysis.

One-way sensitivity analysis

In addition to the probabilistic sensitivity analysis, one-way sensitivity analyses were undertaken to assess the impact of changing input parameter values on the base-case results. This was restricted to parameters where there was uncertainty that the GDG felt could possibly alter the results. Using ranges suggested by the GDG and incorporating the 95% confidence interval (CI), the treatment effect was varied on various outcomes, the short-term utility loss and the cost of treating pre-eclampsia.

Results

Table H.5 shows the results of the deterministic (static) economic model for a cohort of 100 pregnant women. A cohort of 100 was chosen for illustrative purposes representing a typical GP practice.

There were more adverse outcomes in women who did not take aspirin compared with those who did. There were more cases of pre-eclampsia, more babies were delivered before 34 weeks, more babies were SGA and there were more neonatal admissions, all of which require additional NHS resources. The costs of these adverse events offset the initial costs of giving aspirin to all pregnant women at risk of developing pre-eclampsia.

Table H.5 Outcomes in both treatment strategies per 100 pregnant women at risk of developing pre-eclampsia

Outcome	Aspirin	No Aspirin
Pre-eclampsia	7.9	8.7
Delivery < 34 weeks	7.1	7.2
Maternal deaths	0.0	0.0
SGA	11.1	11.3
Neonatal admissions	12.0	12.4
Neonatal deaths	0.49	0.50

SGA = small for gestational age

The total costs per woman were £270,663 for those who received aspirin compared with £278,515 for those not taking aspirin (Table H.6). Aspirin generated less QALY loss compared with no aspirin (13.66 versus 14.18) and was the cheaper strategy overall, resulting in savings of £7,852 per pregnancy and 0.52 additional QALYs per pregnancy. In this scenario, cost effectiveness was unequivocal and aspirin is said to dominate no aspirin in women at risk of developing pre-eclampsia (that is, giving aspirin is cheaper and results in more health benefits). The results demonstrate that, using these baseline data for cost and effectiveness, the policy of giving all pregnant women at risk of developing pre-eclampsia aspirin is cost saving when compared with no aspirin.

Table H.6 The cost effectiveness of aspirin versus no aspirin for a pregnant women at risk of developing pre-eclampsia

Intervention	Costs	Incremental costs	QALYs loss	Incremental QALYs	ICER
No aspirin	£278,515		14.2300		**Dominated**
Aspirin	£270,663	−£7,852	13.7096	−0.520	**Dominant**

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Probabilistic analysis

The results of 1000 iterations of the model are illustrated on the cost-effectiveness/decision plane in Figure H.2. Each point represents the ICER of aspirin compared with no aspirin derived from one iteration of the model and shows that, in 99.8% of the iterations, aspirin was cost saving and resulted in more QALYs, as shown by the close bunching of points in the south-east quadrant. All points lie below the black line that represents the willingness to pay threshold, in this case £20,000/QALY.

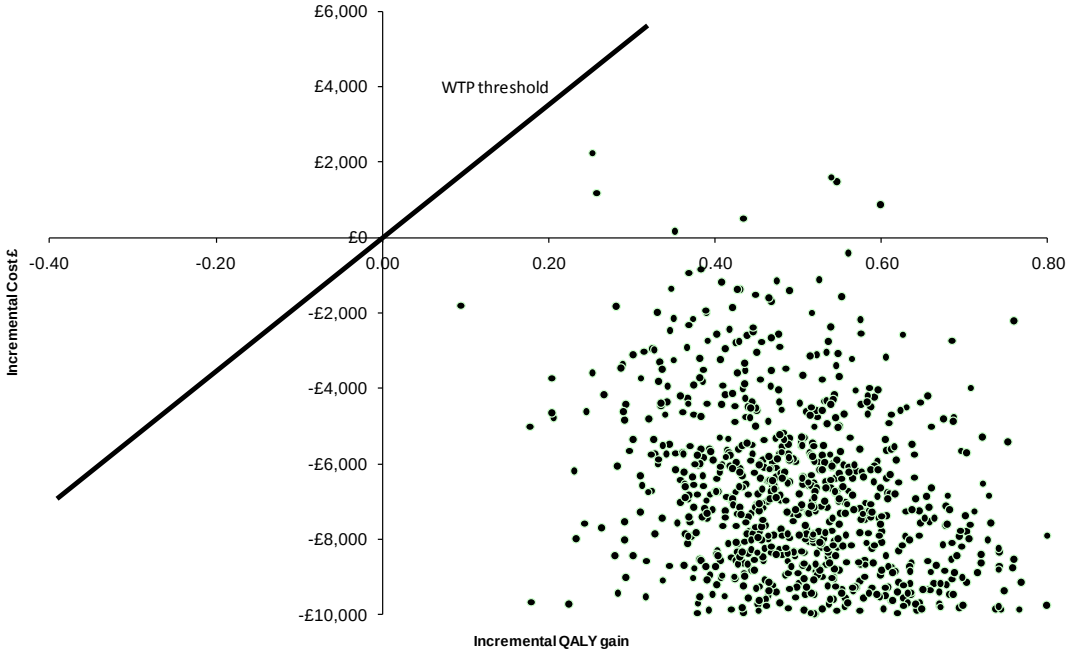

Figure H.2 Cost-effectiveness plane comparing aspirin use in pregnant women at risk of developing pre-eclampsia with no aspirin.

One-way sensitivity analysis

Varying the treatment effect on pre-eclampsia

In the base-case analysis, aspirin was found to reduce the incidence of pre-eclampsia by about 10%. The 95% CI ranged between 84% (lower) to 97% (upper). The 95% CI was used in sensitivity analysis and the results did not change (that is, aspirin was always the preferred strategy). There were more savings and high QALY gain when treatment effects were higher. When the lower values in the CI were put in to the model, the savings increased to around £12,643 per pregnancy and QALY gain to about 0.59 per pregnancy compared with savings of only £2,263 and QALY gain of about 0.44 when a 3% reduction in the incidence of pre-eclampsia was assumed. The effect of treatment effect size on cost savings is shown in Figure H.3.

Varying the aspirin treatment effect on the incidence of neonatal death, maternal death, SGA and birth before 34 weeks (these outcomes were varied one at a time)

Aspirin remained cost saving when treatment effects on neonatal outcomes were varied across the 95% CI. When the lower end of the 95% CI was used (suggesting a bigger treatment effect) the aspirin strategy generated more savings than when the upper end of the CI was used. In all scenarios, the strategy was cost saving. A worst-case scenario was also considered where all parameters were set at their upper limit of the 95% CI at once and the model remained cost saving, although the savings fell from £79 to £19 per person.

Varying the short-term utility loss from pre-eclampsia

In the base case we assumed that short-term utility loss due to pre-eclampsia was the same as that of normotensive pregnant women, which was 3.75%. The GDG suggested a range of 1–15% and this was tested in sensitivity analysis. The results, illustrated in Figure H.4, demonstrate the relationship between short-term utility loss due to pre-eclampsia and overall QALY loss when aspirin is not taken. Aspirin remained dominant even at low short-term utility loss.

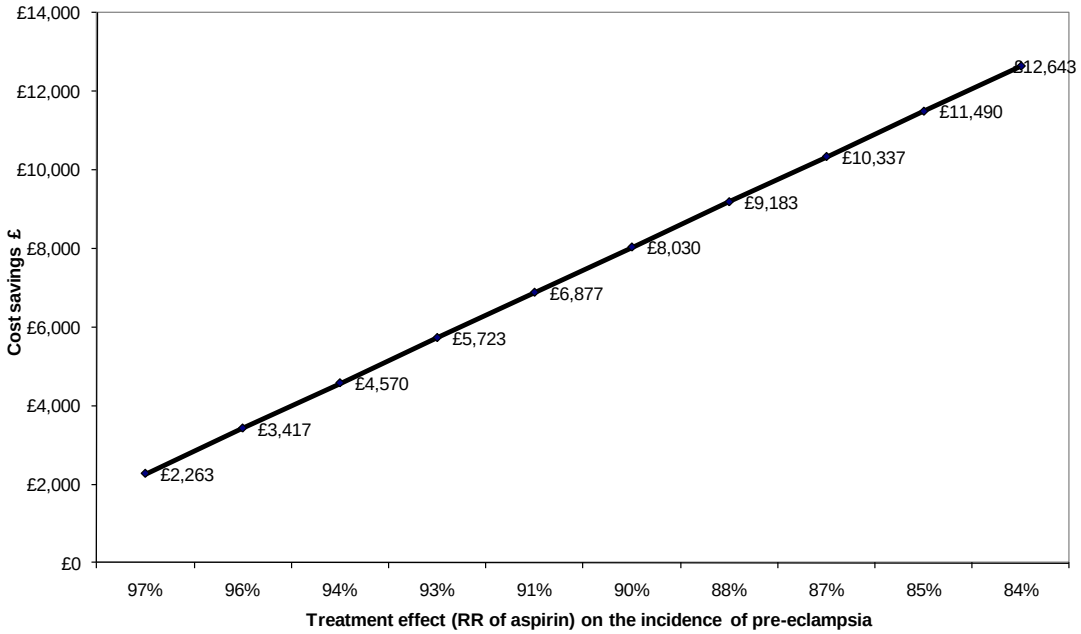

Figure H.3 Sensitivity analysis showing cost savings of aspirin compared with no aspirin in women at risk of developing pre-eclampsia, varying treatment effect on the incidence of pre-eclampsia across the 95% CI (0.84–0.97)

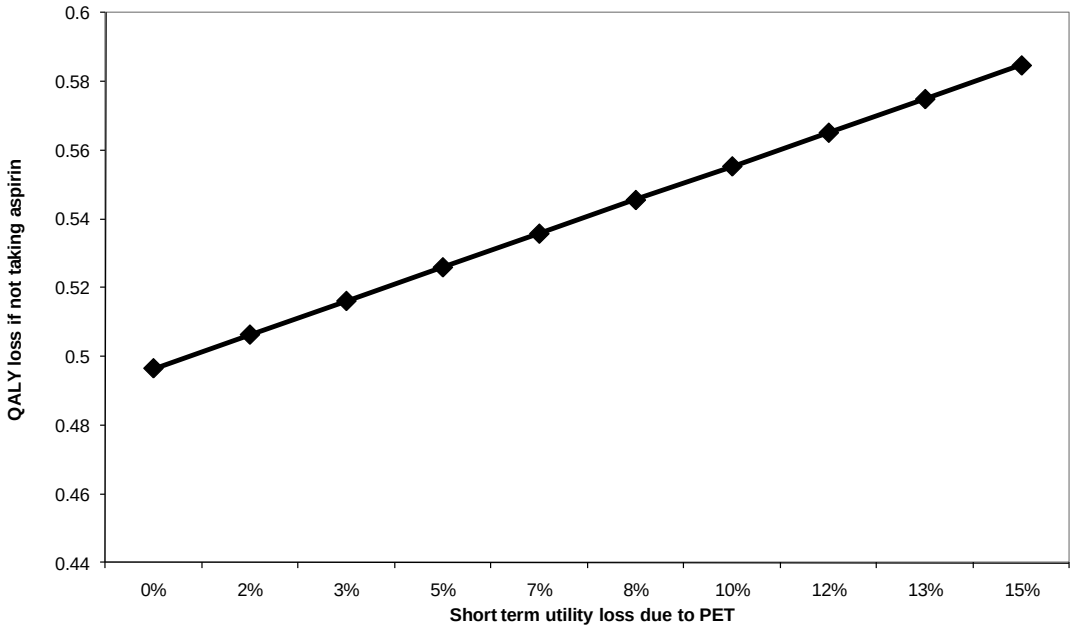

Figure H.4 Sensitivity analysis showing QALY loss for women not taking aspirin compared with those taking aspirin in women at risk of developing pre-eclampsia, varying short-term utility loss from pre-eclampsia over a range suggested by the GDG

Varying the cost of treating pre-eclampsia

The cost of treating pre-eclampsia was varied between £500 and £10,000. The cost of pre-eclampsia did not affect model results across this wide range. There were fewer cases of pre-eclampsia in the aspirin strategy than the no aspirin strategy, meaning that the reduced cost of treating pre-eclampsia more than offset the increased cost of aspirin treatment.

Discussion

The model demonstrated that, in a wide range of scenarios, the aspirin strategy was cost saving compared with a no aspirin strategy for women at risk of developing pre-eclampsia. This is essentially because aspirin is a very low-cost intervention that works effectively. The savings were driven by cost savings due to a lower risk of adverse events requiring hospitalisation in the aspirin group. The model suggested that the aspirin strategy would result in fewer cases of pre-eclampsia, fewer neonatal admissions; fewer women delivering before 34 weeks and fewer SGA babies. Probabilistic sensitivity analysis suggested that there is a 99.8% probability that giving aspirin is cost saving.

The effectiveness data were taken from a high-quality individual-patient meta-analysis. The analysis demonstrated that, on average, aspirin will reduce the incidence of adverse morbidity by about 10%. No published economic evaluations of aspirin in women at risk of pre-eclampsia were identified. However, it is acknowledged that aspirin has been widely evaluated in the cardiovascular field, where it has also been shown to be cost saving.

Quality of life weightings derived from normotensive pregnant women were used. A conservative assumption was also made about the quality of life of women who develop pre-eclampsia, which was assumed to be the same as that seen normotensive women. The GDG felt it was difficult to measure quality of life of children and thus neonatal morbidity was not considered explicitly in this model. A conservate approach was takenn by excluding quality of life of children as this would have strengthened the cost effectiveness of aspirin conclusion. Sensitivity analysis showed that aspirin still generated more QALYs whether the utility loss from pre-eclampsia or pregnancy was low or high.

Conclusion

This model shows that aspirin strategy is cost saving compared with no aspirin in women who are at risk of developing pre-eclampsia across a wide range of assumptions.

Appendix I

Economic analysis of immediate birth (induction of labour) versus expectant management in women with mild to moderate gestational hypertension after 37 weeks of gestation

Introduction

Pregnancy-induced hypertension and pre-eclampsia are common complications of pregnancy. Gestational hypertension complicates 12–15% of all pregnancies, accounting for 25% of all antenatal admissions and over 60% of assessments undertaken in obstetric day-care units.[97] Between 15% and 30% of women with gestational hypertension subsequently develop pre-eclampsia characterised by the development of proteinuria.[97]

There are different resource implications and health consequences for mother and baby for the alternative policies of immediate birth (induction of labour) or expectant management. However, there is currently no evidence on the cost effectiveness of induction of labour in women with mild/moderate gestational hypertension at term compared with expectant management under regular monitoring. In view of the lack of published economic analysis, the GDG requested a *de novo* economic analysis to help in its guideline recommendations.

Methods

The model was developed in Microsoft Excel™ and in TreeAge Pro®. The basic analytical approach is illustrated by the simple schematics in Figures I.1 and I.2, which show the decision sub-trees for immediate birth (induction of labour) versus expectant management in women with mild to moderate gestational hypertension at 37–40 weeks of gestation. Figure I.1 represents a sub-tree for spontaneous onset of labour and induction. Pathways following assisted vaginal birth and emergency caesarean section are the same as those following spontaneous birth. Figure I.2 depicts the sub-tree for planned caesarean section. In both Figure I.1 and I.2, the pathway after neonatal admission is the same, as is that of no admission.

Description of the model

In order to structure the alternative pathways for the economic model, certain simplifying assumptions were made. In the immediate birth pathway, it was assumed that labour is induced within 24–48 hours after admission to hospital. It was also assumed that onset of birth can be spontaneous, by induction or by planned caesarean section. For those that are induced, the choice of induction drug for cervical ripening is intravaginal prostaglandins as recommended in the NICE 'Induction of labour' clinical guideline.[83] Not all women will progress to labour following the use of prostaglandins and in some cases the additional use of oxytocin will be required. It was assumed that 50% of women who did not have planned caesarean section had their induction augmented with oxytocin.[83] Blix *et al.*[244] found that about 50% women will need augmentation with oxytocin after spontaneous onset of labour.

In the expectant management group, it was assumed that onset of birth can be spontaneous, induced or by planned caesarean section. Induction and caesarean section was assumed to happen once the fetal condition no longer justified expectant management. Maternal evaluation consisted

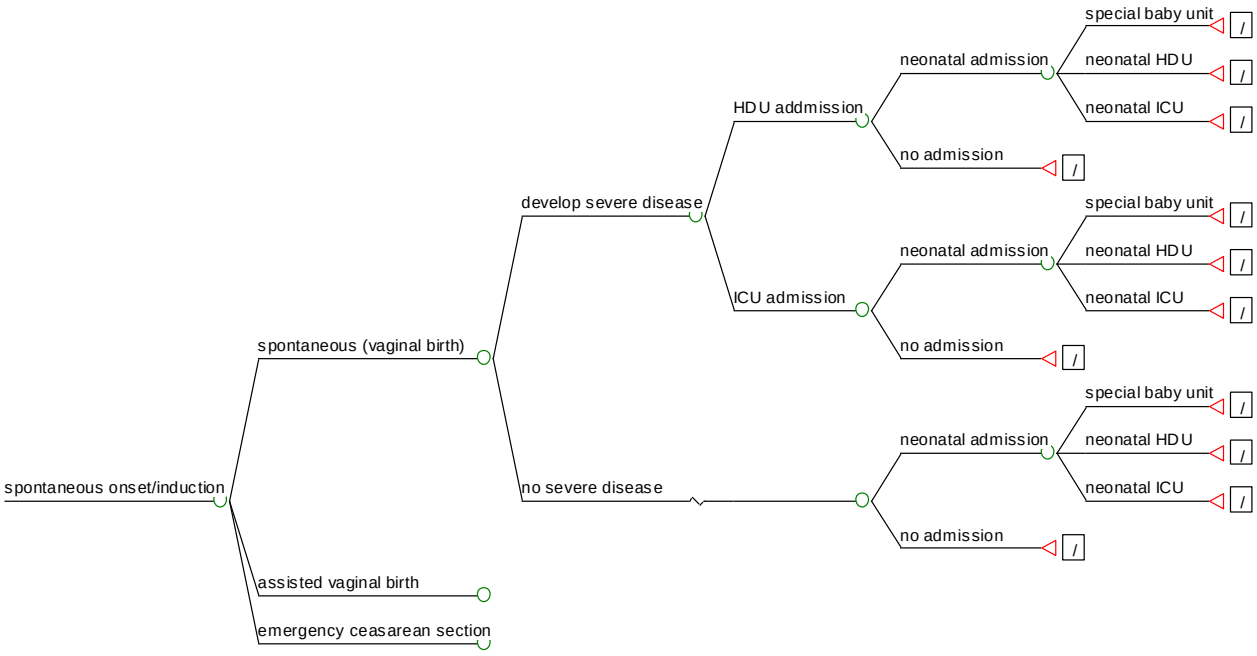

Figure I.1 Spontaneous onset of labour and induction sub-tree for women with gestational hypertension

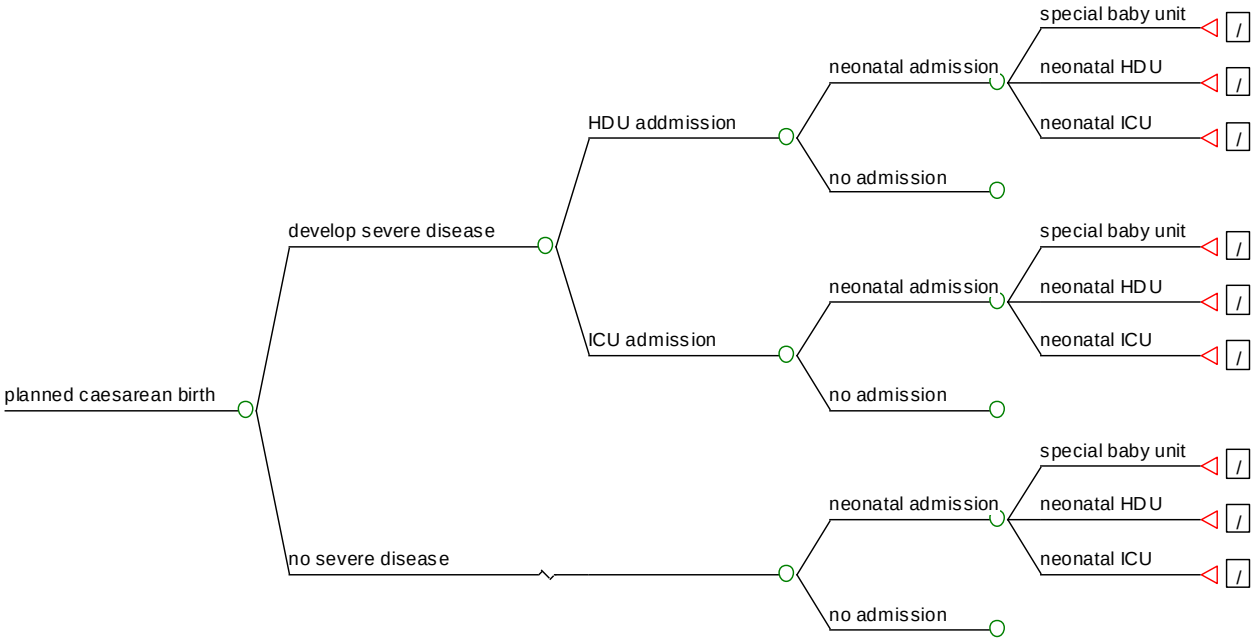

Figure I.2 Planned caesarean section sub-tree for women with gestational hypertension

of frequent evaluation of blood pressure measurements and screening of urine for protein using an automated reagent-strip reading device twice a week (24-hour urine collection for protein in case of a positive dipstick test). Blood tests (platelet count, liver enzymes and renal function) would be performed where there is abnormal maternal blood pressure and/or proteinuria.

In the model, it was assumed that there would be three different modes of birth irrespective of the onset of labour, as reported in the HYPITAT trial.[126] The three different modes of birth were spontaneous vaginal birth, assisted vaginal birth and caesarean section. Caesarean section could be elective (planned) or emergency. Emergency caesarean was assumed to occur in the case of failed induction or after initial spontaneous onset of labour.

Admission to the intensive care (ICU) and high-dependency unit (HDU) was an indication of severity of the disease. Women who developed severe disease were defined in this analysis as those who needed intravenous anticonvulsant medication. It was assumed that all women who did not develop severe disease were managed in the normal maternal ward. Those that developed severe disease were admitted to HDU or ICU. The GDG estimated that 99% of women who developed severe disease would be admitted to HDU while 1% will be admitted to ICU. The HYPITAT trial showed that length of stay in hospital was the same in both strategies, and this model makes the same assumption.

Modelling effectiveness

The effectiveness data were taken from the HYPITAT trial.[126] In the model, the outcomes used were maternal morbidity (development of severe disease defined by the use of intravenous anticonvulsant medication) and neonatal morbidity at term – there were no statistically significant differences between the strategies on neonatal outcomes. However, there was on average one extra day of neonatal admission in the expectant management group, but with fewer admissions to NICU. Tables I.1a and I.1b summarises the data probabilities that were used to populate the model.

Table I.1a Model probabilities for the immediate birth (induction of labour) strategy in women with gestational hypertension

Outcome	Immediate birth	Distribution	Alpha	Beta	Source
Probability of induction onset of labour	97.00%	Beta	366	11	Koopmans *et al.*[126]
Probability of spontaneous onset of labour	2.70%	Beta	10	367	Koopmans *et al.*[126]
Probability of planned caesarean section	0.30%	Beta	1	376	Koopmans *et al.*[126]
Probability of vaginal birth	72.70%	Beta	273	104	Koopmans *et al.*[126]
Probability of assisted vaginal birth	13.30%	Beta	50	327	Koopmans *et al.*[126]
Probability of emergency caesarean section after failed induction	14.00%	Beta	54	323	Koopmans *et al.*[126]
Probability of severe disease needing anticonvulsant medication	6.00%	Beta	24	353	Koopmans *et al.*[126]
Probability of admission to HDU	99.00%	Beta	375	2	GDG
Probability of admission to ICU	1.00%	Beta	4	373	GDG
Probability of neonatal admission	24.00%	Beta	90	287	Koopmans *et al.*[126]
Probability of admission to neonatal medium care	18.00%	Beta	68	309	Koopmans *et al.*[126]
Probability of admission to neonatal HDU	3.00%	Beta	12	365	Koopmans *et al.*[126]
Probability of admission to NICU	3.00%	Beta	10	367	Koopmans *et al.*[126]
Neonatal average length of stay when admitted (days)	3	Deterministic	–	–	Koopmans *et al.*[126]
Proportion needing oxytocin	50%	Deterministic	–	–	GDG and Blix *et al.*[244]

HDU = high-dependency unit; ICU = intensive care unit; NICU = neonatal intensive care unit

Table I.1b Model probabilities for the expectant management strategy in women with gestational hypertension

Outcome	Immediate birth	Distribution	Alpha	Beta	Source
Probability of induction onset of labour	45.40%	Beta	173	206	Koopmans *et al.*[126]
Probability of spontaneous onset of labour	53.00%	Beta	200	179	Koopmans *et al.*[126]
Probability of planned caesarean section	1.60%	Beta	6	373	Koopmans *et al.*[126]
Probability of vaginal birth	68.40%	Beta	253	126	Koopmans *et al.*[126]
Probability of assisted vaginal birth	14.20%	Beta	54	325	Koopmans *et al.*[126]
Probability of emergency caesarean section after failed induction	17.40%	Beta	72	307	Koopmans *et al.*[126]
Probability of severe disease needing anti anticonvulsant medication	12.00%	Beta	46	333	Koopmans *et al.*[126]
Probability of admission to HDU	99.00%	Beta	375	4	GDG
Probability of admission to ICU	1.00%	Beta	4	375	GDG
Probability of neonatal admission	23.00%	Beta	87	292	Koopmans *et al.*[126]
Probability of admission to neonatal medium care	18.00%	Beta	69	310	Koopmans *et al.*[126]
Probability of admission to neonatal HDU	3.00%	Beta	10	369	Koopmans *et al.*[126]
Probability of admission to NICU	2.00%	Beta	8	371	Koopmans *et al.*[126]
Neonatal average length of stay when admitted (days)	3	Deterministic	–	–	Koopmans *et al.*[126]
Proportion needing oxytocin	50%	Deterministic	–	–	GDG and Blix *et al.*[244]

HDU = high-dependency unit; ICU = intensive care unit; NICU = neonatal intensive care unit

Costs

The HYPITAT trial[126] showed that, on average, the immediate birth strategy had mothers delivering 1 week earlier than those in the expectant management group. This meant that the expectant management group incurred an additional 1 week of usual monitoring costs as per the protocol. The average weekly cost per patient with mild to moderate gestational hypertension was £48. The costs included the blood tests and fetal monitoring costs at each visit.

The first-line induction drug was assumed to be prostaglandins. If labour did not begin, women were assumed to be given oxytocin. The cost of two tablets of prostaglandins was £27. For oxytocin, set-up costs of £20 and disposables costs of £7 were assumed. The cost of the drug itself was £3.30.

Costs of the various modes of birth were taken from NHS Reference Costs 2006/07.[240] For the costs of ICU and HDU, the GDG assumed that three organs would need to be supported.* The total cost of a strategy was thus the sum of hospital stay, induction costs and mode of birth, and pre-admission costs for the extra 1 week in the case of the expectant management strategy. In accordance with NICE methods for clinical guidance,[38] a public sector, NHS and Personal Social Services (PSS) perspective was adopted. The model cost inputs are shown in Table I.2.

Valuing outcomes

The economic evaluation[245] that was based on the HYPITAT trial[126] assessed the quality of life using the Medical Outcomes Survey 36 Item Short Form (SF-36), European Quality of Life (EuroQoL), Visual Analogue Scale (VAS), Hospital Anxiety Depression (HADS) and 90 Item Symptom Checklist (SCL-90). The authors found that, at 6 months postpartum, the immediate birth group scored better on the EuroQoL (76.5 in the immediate birth group versus 74.4 in the expectant management group; $P = 0.042$) and on the SCL-90, with 17 complaints compared with 18.2 ($P = 0.044$). Data from the abstract were insufficient to enable its use for the estimation of quality-adjusted life years (QALYs), the preferred unit for outcome for health economic analysis in NICE clinical guidelines.

* NHS costs of ICU/HDU depends on the number of organs being supported. In the model, the GDG suggested that women who are hospitalised owing to pre-eclampsia or its complications have at least three organs supported.

Table I.2 Health service costs incurred by women with gestational hypertension, 2008–09

Outcome	Cost	Source
Normal birth without complications	£1,014	NHS Reference Costs[240]
Instrumental birth with/without complications	£1,440	NHS Reference Costs[240]
Caesarean birth with complications	£3,027	NHS Reference Costs[240]
Caesarean birth without complications	£2,360	NHS Reference Costs[240]
Maternal ward	£586	NHS Reference Costs[240]
HDU, 3 organs supported	£811	NHS Reference Costs[240]
ICU, 3 organs supported	£1,505	NHS Reference Costs[240]
SCBU	£405	NHS Reference Costs[240]
NICU – Level 2	£639	NHS Reference Costs[240]
NICU – Level 1	£939	NHS Reference Costs[240]
3 mg dinoprostone (per tablet)	£106.23 for 8 tablets @ £13.28	*British National Formulary*[198]
10 mg dinoprostone pessary (within retrieval device)	£30.00	*British National Formulary*[198]
1 mg dinoprostone vaginal gel	£13.28	*British National Formulary*[198]
2 mg dinoprostone vaginal gel	£13.28	*British National Formulary*[198]
Oxytocin, 3 × 10 units/ml, 1 ml ampoule	£3.03	*British National Formulary*[198]
Staff costs for setting up oxytocin	£20.00	*British National Formulary*[198]
Disposables	£7.00	*British National Formulary*[198]
Magnesium sulphate (intravenous)[a]	4 mg £2.75 2 mg £6.40	*British National Formulary*[198]
Labetalol (intravenous)	£2.12	*British National Formulary*[198]
1 week of monitoring before admission	£48	Calculated

HDU = high-dependency unit; ICU = intensive care unit; NICU = neonatal intensive care unit; SCBU = special care baby unit

[a] One dose of 4 mg and then 2 mg hourly for at least 24 hours

The Harvard Cost-Effectiveness Registry was searched but no quality of life values associated with mild/moderate gestational hypertension and development of severe disease were found. It was therefore assumed that women who had gestational hypertension had the same quality of life as normotensive pregnant women, based on GDG opinion, while those who developed severe disease were assumed to have the same quality of life as people who had been admitted to ICU/HDU for any reason.

A study by Sonnenberg *et al.*[243] was identified that had useful outcome data and that evaluated the cost effectiveness of contraception methods in women of average health and fertility, ranging from 15 to 50 years of age, compared with non-use of contraception. The authors found that short-term utility loss due to pregnancy was 0.0375. A study by Edwards *et al.*[246] was identified that compared the cost effectiveness of meropenem with that of imipenem plus cilastatin in the treatment of severe infections in hospital intensive care in the UK. The study estimated that the quality of life weight for someone who has stayed in intensive care is about 0.712. This weight was used in the model for those who developed severe disease. The overall quality of life weighting was assumed to be the product of the severity of disease and the general pregnancy for those that developed severe disease; those who did not develop severe disease had the quality of life weighting associated with general pregnancy. The QALYs are shown in Table I.3.

Table I.3 Quality of life weights assigned to pregnant women and neonatal death (QALYs)

Health state	QALY	Source
Normotensive pregnant women	0.69[a]	Sonnenberg *et al.*[243]
Severe complications of pre-eclampsia	0.019[b]	Edwards *et al.*[246]

[a] The QALY gains were derived from data taken from the study by Sonnenberg *et al.*[243] that found that the quality of life weight for pregnancy was 0.9625; to convert this to a QALY gain, the weight was divided by 52 to get a weekly QALY, and then multiplied by 38 for those who delivered at term

[b] QALY data for those who developed severe disease were taken from Edwards *et al.*[246] The figure in the text was divided by 52 to get a weekly weight. It was assumed that the women they will stay in ICU/HDU for a maximum of 2 weeks, and thus the weekly weight was multipled by 2 to get the weight for severe disease used in the model

Sensitivity analysis

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was undertaken to explore to what extent the results were affected by the uncertainty surrounding the model input parameters. In PSA, each model parameter is assigned a distribution reflecting the expected sampling variation, and the costs and effects are determined after simultaneously selecting random values from each distribution. The process is repeated many times in a Monte Carlo simulation to give an indication of the extent to which model input parameter uncertainty affects the incremental cost-effectiveness ratio (ICER). Distributions were not applied to cost parameters as there was generally little uncertainty associated with this data.

One-way sensitivity analysis

In addition to the PSA, one-way sensitivity analyses were undertaken to assess the impact of changing input parameter values on the base-case results. The parameters that were varied were those that the GDG felt could possibly change model conclusions across ranges suggested by the GDG. These included the incidence of severe disease, quality of life estimates, neonatal admission rates and pre-admission monitoring costs.

Results

Table I.4 shows that, with the baseline assumptions set out above, immediate birth generates savings of about £213 per women with mild to moderate gestational hypertension when compared with expectant management, and generates 0.04 more QALYs. In such instances where one intervention is both cheaper and more effective, the ICER is not calculated because of the concept of dominance. The results demonstrate that, overall, the policy of immediate birth is less costly and more effective when compared with expectant management in women with mild to moderate gestational hypertension at term.

Table I.4 Cost effectiveness of immediate birth compared with expectant management in women with mild to moderate gestational hypertension at term

	Costs	QALY gain	Incremental costs/savings	Incremental QALYs	ICERs
Expectant management	£2,988	0.628	–£213	–	Dominated
Immediate birth	£2,774	0.669	–	0.04	Dominant

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Probabilistic analysis

The results of 1000 iterations of the model are illustrated on the cost-effectiveness/decision plane in Figure I.3. Each point represents the ICER of immediate birth compared with expectant management derived from one iteration of the model. It can be seen that, in 99% of the iterations, immediate birth was cost saving or and resulted in more QALYs, as shown by the close bunching of points in the south-east quadrant. In this decision plane, all points lie below the thick diagonal line that represents the willingness to pay threshold, in this case £20,000/QALY. Overall, all points lie below the willingness to pay line in the north-east or south-east quadrant, suggesting that immediate birth is cost effective at all times (100%).

One-way sensitivity analysis

Varying the incidence of spontaneous onset of labour in the expectant management strategy

Spontaneous onset of labour rates have an effect on the mode of delivery as many are likely to deliver vaginally, which is cheaper and is associated with better quality of life compared with other modes of birth. The spontaneous onset of labour rate was varied in this sensitivity analysis between 40% and an upper limit of 80%. However, in this analysis the base-case conclusions (of dominance) were unaltered (see Figure I.4).

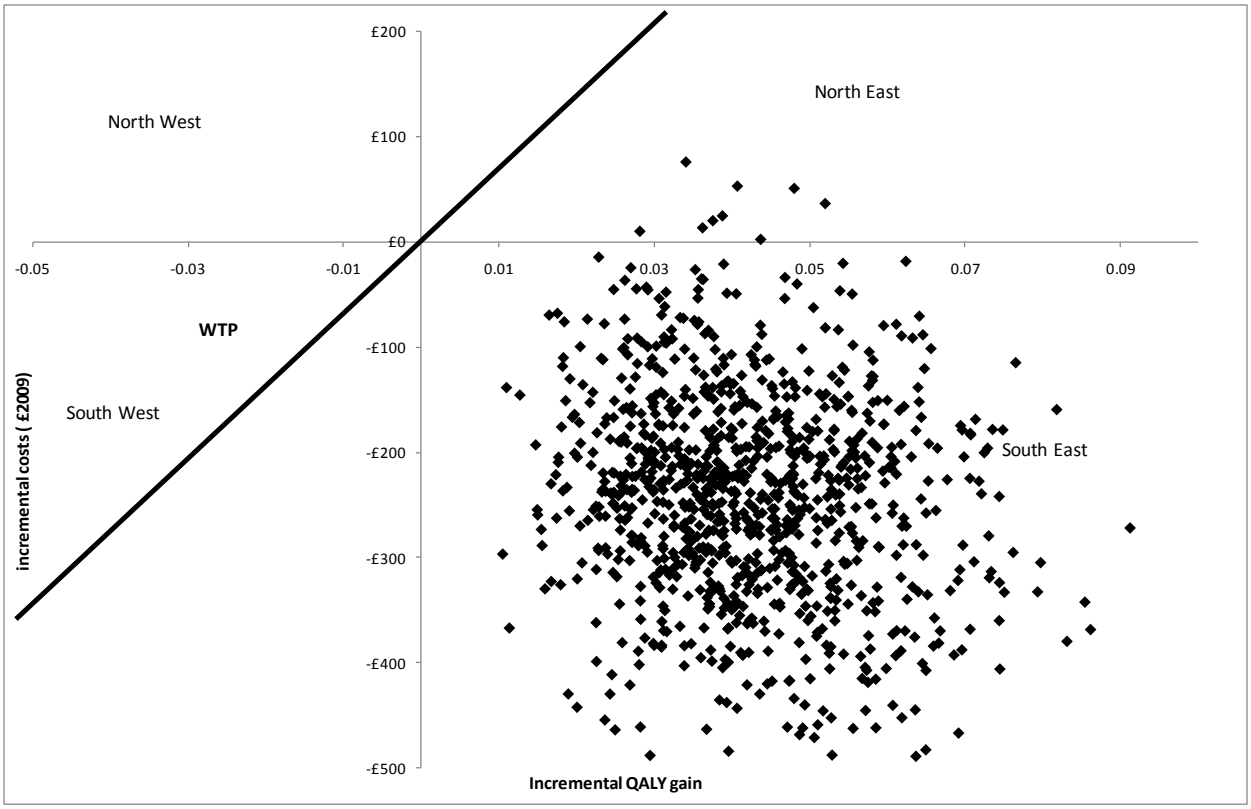

Figure I.3 Cost-effectiveness plane comparing immediate birth with expectant management in women with mild to moderate gestational hypertension at term

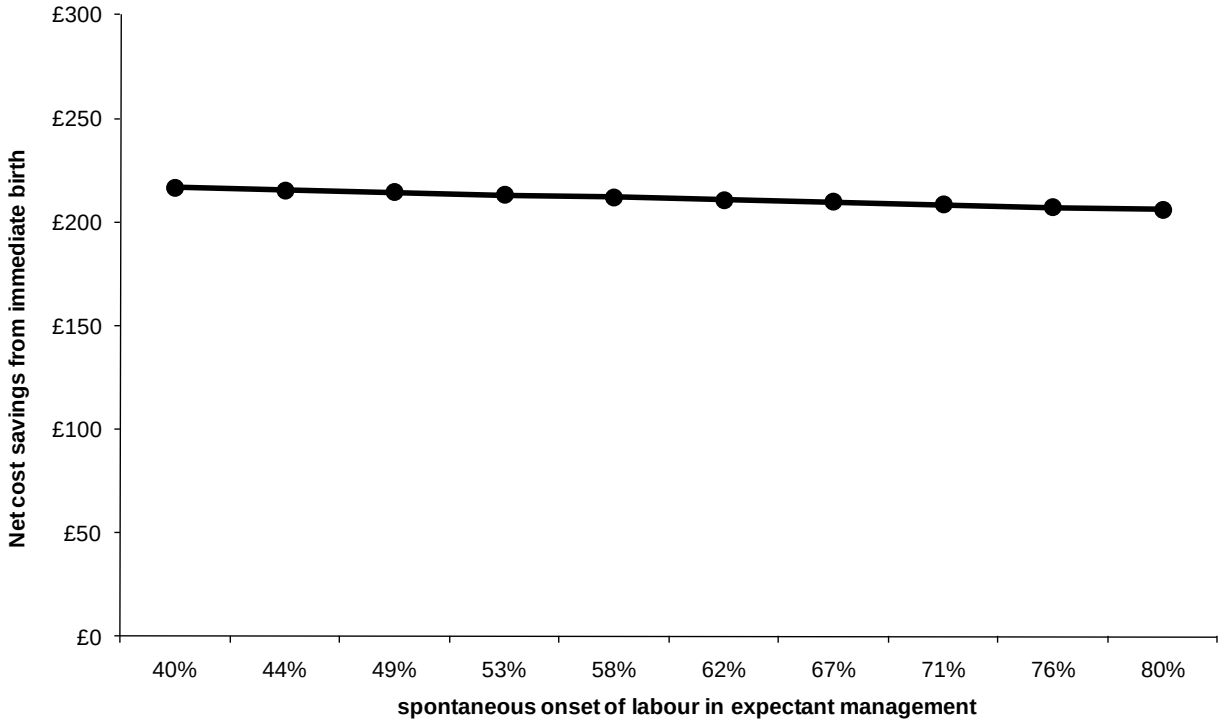

Figure I.4 Sensitivity analysis showing cost savings from immediate birth, varying the incidence of spontaneous onset of labour in the expectant management strategy

Varying the incidence of severe disease in the expectant management strategy, QALY gain/loss

The incidence of severe disease has an impact on costs and QALYs since in the model only those who developed severe disease were hospitalised in the HDU and ICU, with additional costs of anticonvulsant medication. The incidence of severe disease using expectant management was varied between 5% and 15%. Figure I.5 shows that the model was sensitive to changes in this assumption. If it is assumed that there is no difference in the incidence of severe disease between the strategies (an unlikely scenario), the immediate birth option will no longer be dominant as it will result in fewer QALYs compared with expectant management. However, as long as there is a positive difference in the incidence of severe disease, immediate birth generates more QALYs. The cost savings are also less when the incidence of severe disease is assumed to be low and more when it is assumed to be high in the expectant management strategy.

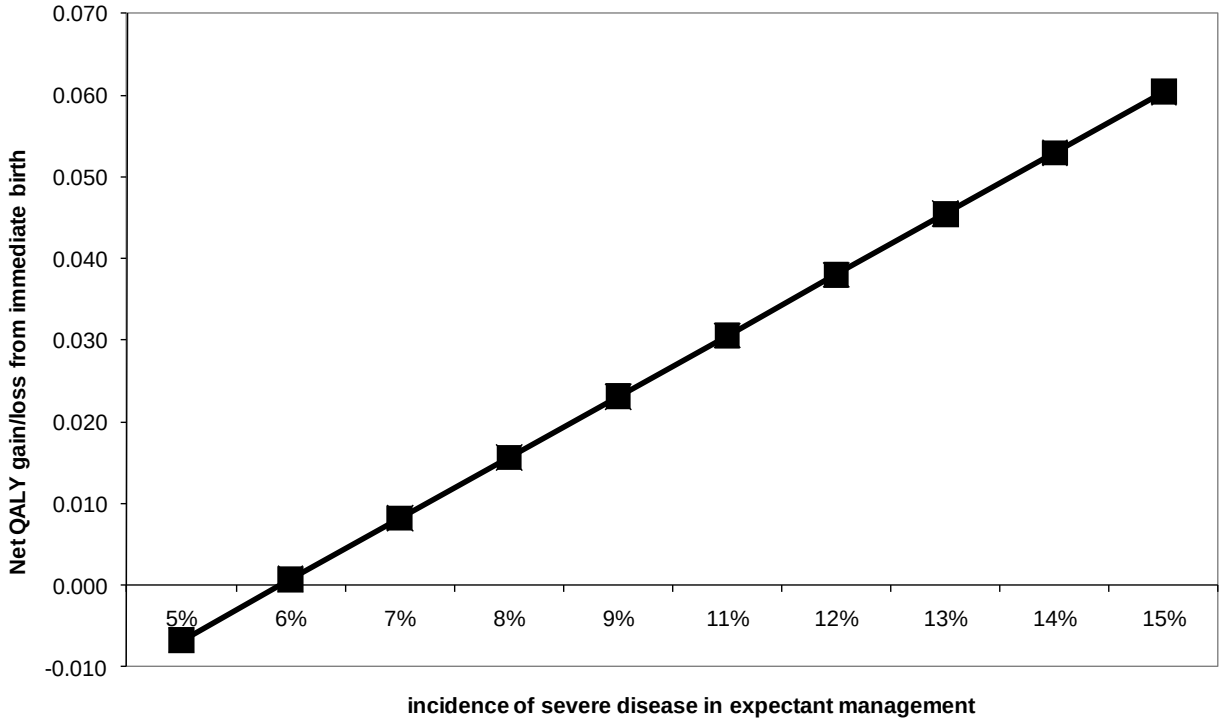

Figure I.5 Sensitivity analysis showing net QALY gain from immediate birth, varying the incidence of severe disease in the expectant management strategy

Varying incidence of emergency caesarean section in the expectant management strategy (caesarean section)

The caesarean section rates in the expectant management strategy were varied between 5% and 25%, holding caesarean section rates with immediate birth constant. Again, the model results did not change: immediate birth remained dominant in all cases, generating more QALYs at a cheaper cost overall except when the rates were assumed to be as low as 5% (it is highly unlikely in practice that emergency caesarean section rates of expectant management will be lower than those of immediate birth in this population). In this scenario, immediate birth, although not cost saving, was still the most cost-effective option, with an estimated ICER of about £760/QALY. Figure I.6 shows the change in net costs as the incidence of emergency caesarean section in the expectant management strategy is varied.

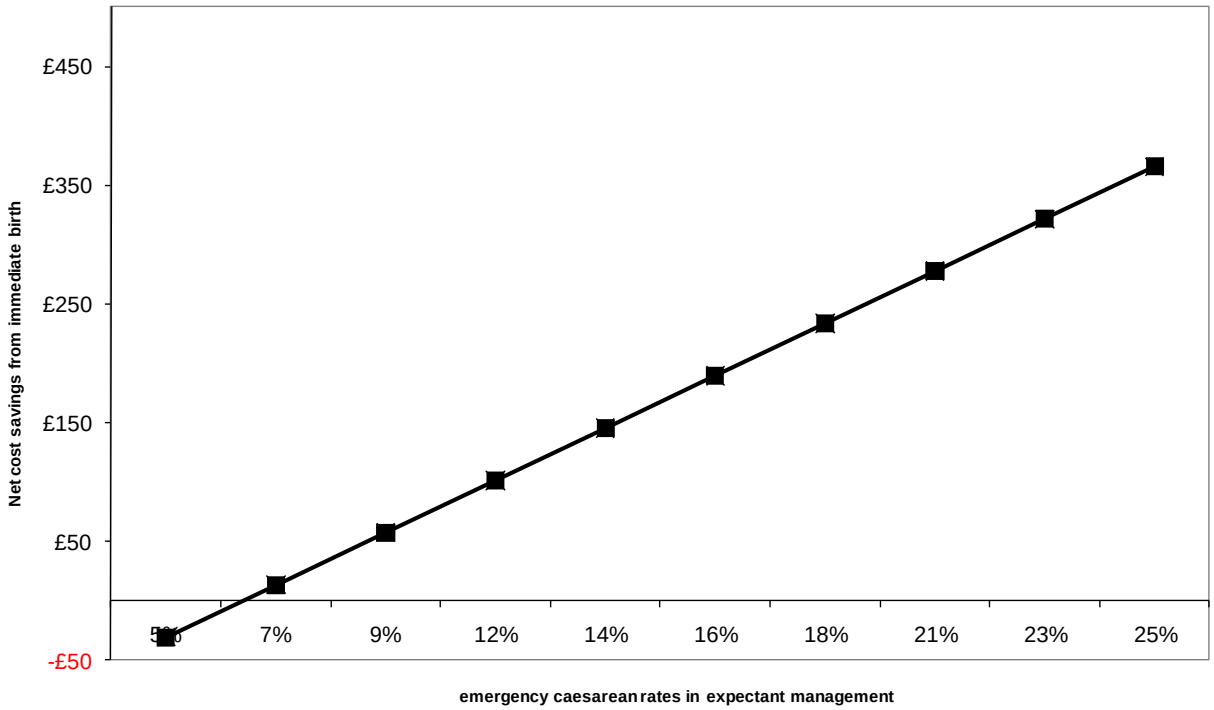

Figure I.6 Sensitivity analysis showing cost savings from immediate birth, varying incidence of emergency caesarean section in the expectant management strategy

Varying the pre-admission monitoring costs in the expectant management strategy

Most of the cost assumptions were not subjected to sensitivity analysis as it was felt that there was not much uncertainty associated with NHS reference costs.[240] However, the cost of weekly monitoring cost prior to admission in the expectant management strategy was varied. The average weekly cost was estimated to be about £48 for women with mild to moderate gestational hypertension. The average weekly monitoring cost was varied between £20 and £60. Cost effectiveness was not affected but this analysis showed that increased monitoring costs led to greater savings with immediate birth.

Discussion

This analysis suggests that immediate birth dominates expectant management in that it results in better maternal outcomes and is less costly in women with mild to moderate gestational hypertension. The mean cost per patient for the immediate birth strategy was estimated to be about £2,774, compared with about £2,990 for expectant management. This results in savings of about £213 per patient. The savings per case can mean large savings at an institutional or national level. For example, a primary care trust with about 1000 women with mild to moderate gestational hypertension could save around £213,000 per year. The robustness of the base-case results were tested using both probabilistic and univariate sensitivity analysis and it was found that these changes in input parameters did not affect the base-case conclusions. Probabilistic sensitivity analysis showed that immediate birth will always generate more net health benefit when compared with expectant management.

No published economic studies that have compared immediate birth strategy with expectant management strategy in women with mild to moderate gestational hypertension at term were identifed. However, the results are comparable to those in an economic abstract of the HYPITAT study presented in Washington,DC, by Vijgen *et al.*[247] in September 2008. The authors found that the costs were €5,399 and €6,025 for immediate birth and expectant management, respectively, with a net saving of €626. They also concluded that the quality of life of women in

the immediate birth strategy was better when compared with expectant management, hence technically a result of dominance.

Effectiveness data were taken from the HYPITAT trial done in the Netherlands. The trial found a statistically significant difference in composite maternal adverse effects (RR 0.71; 95% CI 0.59 to 0.86). However, when the outcomes were disaggregated, most of the individual components were not statistically significant. For instance, in the immediate birth group, the incidence of HELLP syndrome was 1% compared with 3% in expectant management group but the confidence intervals were wide and not statistically significant. This may suggest that at least some of the difference found between the strategies could be due to chance. However, the use of intravenous anticonvulsant medication, which indicates the development of severe disease, was reduced by almost 50% when women were induced than when they were managed expectantly and this was statistically significant. The model was sensitive to changes in assumptions about the incidence of severe disease. The GDG noted that this was not surprising given that those who developed severe disease needed to be hospitalised in HDU or ICU, which has considerable resource implications.

The GDG is also aware of the limitations of the HYPITAT study, especially in the management of blood pressure. The GDG noted that if the trial were to be repeated in the UK setting where blood pressure is managed more aggressively than in the Netherlands, there may be little to choose between immediate birth and expectant management. The GDG thus considers that the results of the model should be interpreted with this specific caveat in mind.

QALY values are not an important driver of results, given that immediate birth is cost saving. However, quality of life weightings derived from pregnant women without gestational hypertension and those hospitalised in ICU for any other reason may not accurately approximate those for women with gestational hypertension or complications of pre-eclampsia. Sensitivity analysis using different quality of life weights did not alter the cost-effectiveness outcome.

Conclusion

The model suggests that an immediate birth strategy is cost effective (cost saving) when compared with an expectant management strategy in women with mild to moderate gestational hypertension. However, the GDG noted that this result needs to be interpreted with caution as it is largely driven by the incidence of severe disease that tends to occur less if blood pressure is managed as has been recommended in this guideline.

Appendix J

Economic analysis of immediate birth (induction of labour) versus expectant management in women who have pre-eclampsia with mild or moderate hypertension at 34–37 weeks of gestation

Economic Question

What is the cost effectiveness of immediate birth by planned induction of labour (henceforth 'immediate birth') compared with expectant management in women who have pre-eclampsia with mild or moderate hypertension of 34–37 weeks of gestation?

There are different resource implications and health consequences for mother and baby for these alternative policies. However, there is currently no evidence on the cost effectiveness of induction of labour in women who have pre-eclampsia with mild or moderate hypertension preterm compared with expectant management under regular monitoring. In view of this, the GDG requested a *de novo* economic analysis to help in its guideline recommendations.

Methods

The methods used are the same as those described for the term model (see Appendix I), except that this population consists of pregnant women who already have mild/moderate pre-eclampsia. In this population it has been recommended that there is no need to repeat quantification of proteinuria.

Model structure and assumptions

The model was developed in Microsoft Excel™ and in TreeAge Pro®. The basic analytical approach is illustrated by the simple schematic in Figures J.1 and J.2 showing the decision tree for immediate birth (induction of labour) versus expectant management in women with mild to moderate gestational hypertension at 34–37 weeks of gestation. Pathways following assisted vaginal birth and emergency caesarean section are the same as those following spontaneous birth. Figure J.1 represents a sub-tree for spontaneous onset of labour and induction. Figure J.2 depicts the sub-tree for planned caesarean section.

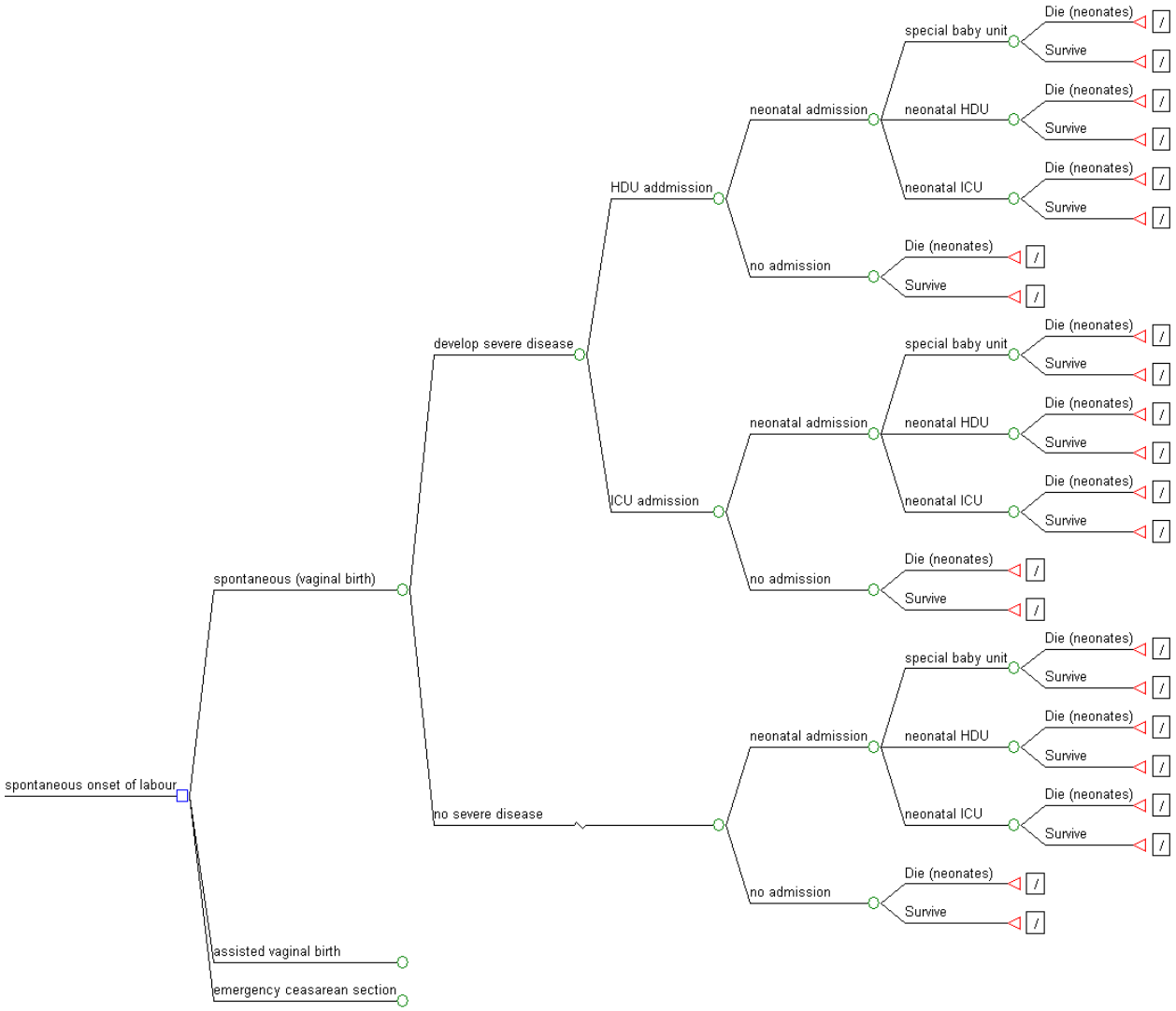

Figure J.1 Spontaneous onset of labour and induction sub-tree for women with gestational hypertension

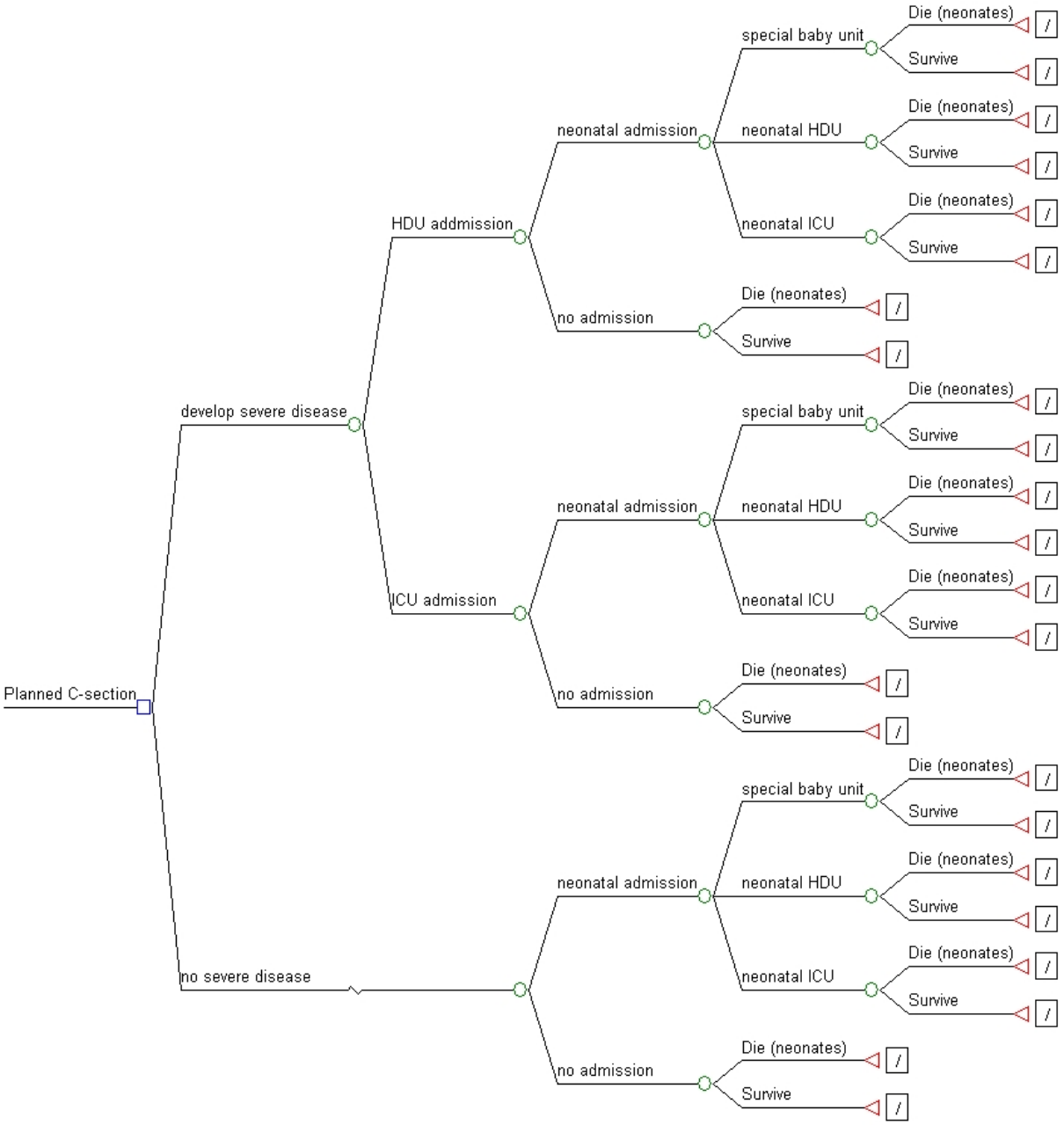

Figure J.2 Planned caesarean section sub-tree for women with gestational hypertension

Modelling effectiveness

There are no published effectiveness trials comparing immediate birth with expectant management in women with mild/moderate pre-eclampsia at 34–37 weeks of gestation. Two trials were found that compared the two policies before 34 weeks of gestation, which showed a clear association between immediate preterm birth and increased neonatal morbidity with no apparent decrease in maternal morbidity in women with severe pre-eclampsia.[145,138] Evidence from women with gestational hypertension at term, however, showed no difference in neonatal outcomes as all babies will have matured.[126]

Owing to the lack of randomised trials in women with mild to moderate pre-eclampsia, for gestational age 34–37 weeks, data were taken from a retrospective case–control study in the USA by Habli *et al.*[145] The study was a secondary analysis of neonatal outcomes by week of delivery between 35 and 37 weeks of gestation. The neonatal outcomes included the

percentage of babies requiring NICU admission, the mean duration of neonatal hospitalisation and the proportion of babies with neonatal complications. Neonatal outcomes for the immediate birth arm of the model were those reported at 35 weeks. The outcomes for expectant management were assumed to be those reported in weeks 36 and 37.

In the model, it is assumed that neonates who needed mechanical ventilation are managed in a high-dependency unit (HDU) and those who did not are managed in a special care baby unit (SCBU). Neonates with no complications are managed in the normal maternity ward.

Maternal morbidity (development of severe disease defined by the use of intravenous anticonvulsant medication) in women with pre-eclampsia was taken from Barton *et al.*[96] The GDG considered that severe morbidity was likely to be a rare event in women who are induced. However, they acknowledged that the disease can develop after giving birth and consequently estimated that about 1% of women develop severe disease in this group. Model probabilities are given in Table J.1.

Table J.1 Model probabilities used in the model by strategy in women with gestational hypertension

Outcome	Immediate birth	Expectant management	Source
Probability of induction onset of labour	95.0%	60.0%	Habli *et al.*[145]
Probability of spontaneous onset of labour	0.0%	36.0%	Habli *et al.*[145]
Probability of planned caesarean section	5.0%	4.0%	Habli *et al.*[145]
Probability of vaginal birth	75.0%	75.0%	Boulvain *et al.*[248]
Probability of assisted vaginal birth	15.0%	15.0%	Boulvain *et al.*[248]
Probability of emergency caesarean section after failed induction	10.0%	10.0%	Boulvain *et al.*[248]
Probability of severe disease needing anticonvulsant medication	1.0%	20.0%	GDG
Probability of admission to HDU	99.0%	99.0%	GDG
Probability of admission to ICU	1.0%	1.0%	GDG
Probability of neonatal admission	57.14%	33.33%	Habli *et al.*[145]
Probability of admission to neonatal medium care	42.86%	66.67%	Habli *et al.*[145]
Probability of admission to neonatal HDU	50.0%	57.14%	Habli *et al.*[145]
Probability of admission to NICU	50.0%	42.86%	Habli *et al.*[145]
Proportion needing oxytocin	47.5	48	Calculated
Neonatal average length of stay when admitted (days)	4.9	4.2	Habli *et al.*[145]
Proportion needing oxytocin	50%	50%	GDG and Blix *et al.*[244]

HDU = high-dependency unit; ICU = intensive care unit; NICU = neonatal intensive care unit

Modelling costs

In accordance with NICE methods for clinical guidance,[38] a public sector, NHS and Personal Social Services (PSS) perspective was adopted.

The HYPITAT trial[126] showed that, on average, the immediate birth strategy had mothers delivering 1 week earlier than in the expectant management group at term. This meant that the expectant management group incurred an additional 1 week of usual monitoring costs as per the protocol. The average weekly costs per patient with mild to moderate pre-eclampsia were estimated to be £617. This was calculated assuming that, on average, women with moderate pre-eclampsia are hospitalised for at least 4 days and managed as outpatients for the rest of the week, while those with mild pre-eclampsia are admitted for at least 1 day. It was assumed that the women managed expectantly will deliver a week later than those who are induced immediately.

The first-line induction drug was assumed to be prostaglandins. If labour did not begin, women were assumed to be given oxytocin. The cost of two tablets of prostaglandins was £27. For oxytocin, set-up costs of £20 and disposables costs of £7 were assumed. The cost of the drug itself was £3.30. Women in the immediate birth arm were given two doses of intravenous dexamethasone (steroids) of 12 mg each. One dose costs £14.64 and hence the two doses cost £29.28.

The costs of the various modes of birth were taken from NHS Reference Costs 2006/07.[240] For the costs of ICU and HDU, the GDG assumed that three organs would need to be supported. For women who did not develop severe disease, it was assumed that they remained in the general maternity ward. Only those who developed severe disease were assumed to be referred to HDU or ICU. The total cost of a strategy was thus the sum of hospital stay, induction costs,and mode of birth, and pre-admission costs for the extra 1 week in the case of the expectant management strategy. Model costs are shown in Table J.2.

Table J.2 Health service costs incurred by women who have pre-eclampsia with mild or moderate hypertension, 2008–09

Outcome	Cost	Source	Notes
Normal birth without complications	£1,014	NHS Reference Costs[240]	
Instrumental birth with/without complications	£1,440	NHS Reference Costs[240]	
Caesarean birth with complications	£3,027	NHS Reference Costs[240]	
Caesarean birth without complications	£2,360	NHS Reference Costs[240]	
Maternal ward	£175	NHS Reference Costs[240]	Per day
HDU, 3 organs supported	£811	NHS Reference Costs[240]	
ICU, 3 organs supported	£1,505	NHS Reference Costs[240]	
SCBU	£405	NHS Reference Costs[240]	
NICU – Level 2	£639	NHS Reference Costs[240]	
NICU – Level 1	£939	NHS Reference Costs[240]	
3 mg dinoprostone (per tablet)	£106.23	*British National Formulary*[198]	8 tablets at £13.28 each
10 mg dinoprostone pessary (within retrieval device)	£30.00	*British National Formulary*[198]	
1 mg dinoprostone vaginal gel	£13.28	*British National Formulary*[198]	
2 mg dinoprostone vaginal gel	£13.28	*British National Formulary*[198]	
Oxytocin, 3 × 10 units/ml, 1 ml ampoule	£3.03	*British National Formulary*[198]	
Staff costs for setting up oxytocin	£20.00	*British National Formulary*[198]	
Disposables	£7.00	*British National Formulary*[198]	
Magnesium sulphate (intravenous)	4 mg £2.75 2 mg £6.40	*British National Formulary*[198]	1 dose of 4 mg and then 2 mg hourly for at least 24 hours
Labetalol (intravenous)	£2.12	*British National Formulary*[198]	
1 week of monitoring before admission	£617	Calculated	
Dexamethasone (4 mg costs £1.22)	£14.28	*British National Formulary*[198]	2 doses of 12 mg each

HDU = high-dependency unit; ICU = intensive care unit; NICU = neonatal intensive care unit; SCBU = special care baby unit

Valuing outcomes

See the discussion in Appendix I on valuing outcomes.

Sensitivity analysis

One-way sensitivity analyses were undertaken to assess the impact of changing input parameter values on the base-case results. The parameters that were varied were those that the GDG felt could possibly change model conclusions, across ranges suggested by the GDG. These included the incidence of severe disease, quality of life estimates, neonatal admission rates and pre-admission monitoring costs.

Results

Table J.3 shows the total costs and QALYs of pregnancy for women with mild to moderate pre-eclampsia. For the immediate birth and the expectant management strategies, the average total costs are £4,301 and £4,114, respectively. Immediate birth generates 28.305 QALYs compared with 28.240 QALYs for the expectant management strategy. The incremental costs of immediate birth over expectant management are estimated to be £187. However, immediate birth generates 0.065 extra QALYs compared with expectant management. The estimated incremental cost-effectiveness ratio (ICER) is about £2,900 per QALY. The results suggest that the policy of immediate birth is cost effective when compared with expectant management in women with mild to moderate pre-eclampsia preterm.

Table J.3 Cost effectiveness of immediate birth compared with expectant management in women with mild to moderate pre-eclampsia preterm

	Costs	QALY gain	Incremental costs	Incremental QALYs	ICERs
Expectant management	£4,114	28.240	–	–	–
Immediate birth	£4,301	28.305	£187	0.065	£2,901

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Sensitivity analysis

Varying the incidence of spontaneous onset of labour in the expectant management strategy

In this analysis, the spontaneous onset of labour rate with expectant management was varied between 20% and 80%. Immediate birth remained cost effective with favorable ICERs for immediate birth. At a rate of 20%, the ICER was £1,640 per QALY, and this only rose to £6,369 per QALY when a rate of 80% was assumed. This is not surprising, given that 75% of women who have spontaneous onset of labour give birth vaginally, which is cheaper than assisted birth or caesarean section.

Varying the incidence of severe disease in the expectant management strategy

The incidence of severe disease has an impact on costs and the QALYs since in the model only those who developed severe disease were hospitalised in the HDU and ICU, with additional costs of anticonvulsant medication. The incidence of severe disease using expectant management was varied between 2% (suggesting there was little difference compared with immediate birth) and 30%. Figure J.3 shows that the model was highly sensitive to changes in this parameter. If it is assumed that there is a small difference, i.e. 2%, in the incidence of severe disease between the strategies, immediate birth is dominated by expectant management. Even if the incidence of severe disease in the expectant management arm is 12%, immediate birth is not cost effective at a £20,000/QALY threshold. The immediate birth strategy becomes cost effective if the incidence of severe disease in the expectant management group is 13% and above. The bigger the difference in incidence of severe disease between the strategies, the more attractive it is to offer birth immediately in women with mild to moderate pre-eclampsia.

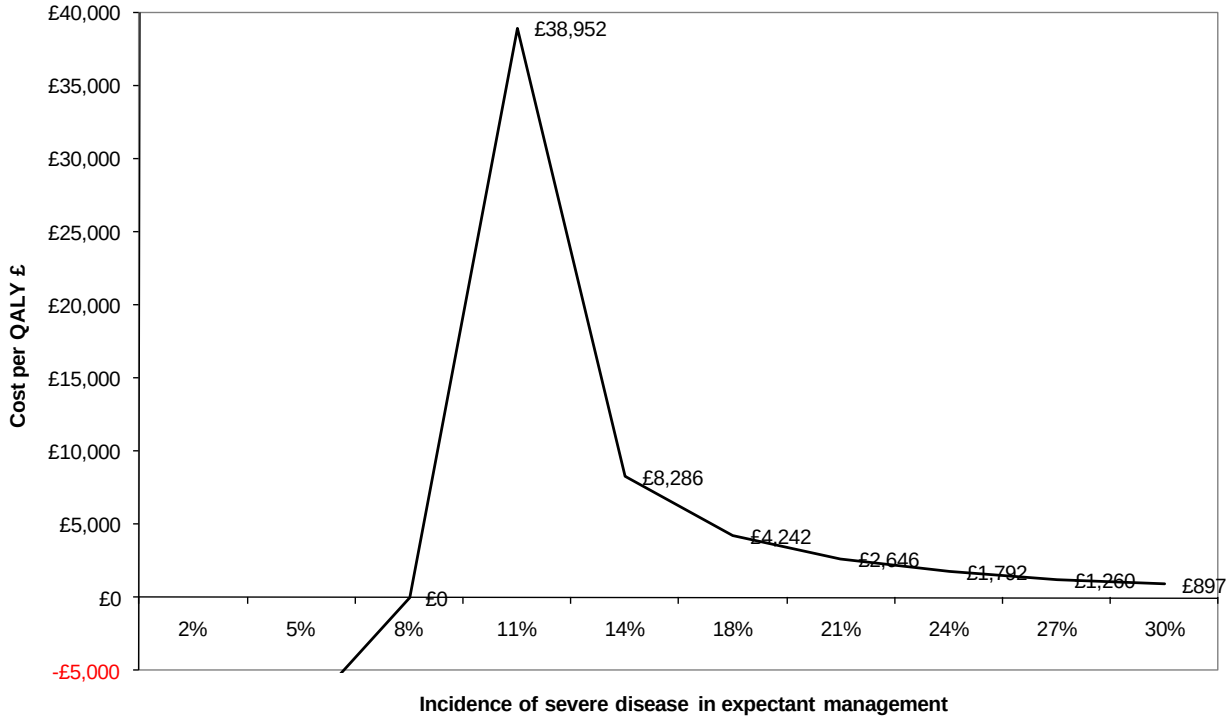

Figure J.3 Sensitivity analysis showing cost savings of immediate birth compared with expectant management in women with mild/moderate pre-eclampsia preterm, varying the incidence of severe disease in the expectant management strategy

Varying the incidence of emergency caesarean section after spontaneous onset of labour in the expectant management strategy

Rates of emergency caesarean section after spontaneous labour were varied between 5% and 30%. In the immediate birth strategy it was assumed that there was no spontaneous onset of labour: women were either induced or had planned caesarean section. Immediate birth remained cost effective across the range of the values tested. Changing the incidence did not alter the base-case conclusion that immediate birth was cost effective when compared with expectant management in women with mild to moderate pre-eclampsia.

Varying the pre-admission monitoring costs in the expectant management strategy

The average weekly cost of monitoring prior to admission in the expectant management strategy was varied between £100 and £650. At a monitoring cost as low as £100 per week, the ICER rose to about £11,000/QALY, still suggesting that immediate birth was cost effective. The conclusions are not sensitive to changes in monitoring costs (Figure J.4).

Varying the neonatal admission rate in the expectant management strategy

In the base model, admission rates in the immediate birth strategy were about 57% compared with 33% in the expectant management strategy.

Neonatal admissions have an impact on costs since the cost of SCBU and ICU is more expensive compared with the general ward, and has an impact on the quality of life of mothers who are separated from their babies. Neonatal admission rates in the expectant management strategy were varied between 20% and 50%. At a neonatal admission rate of 20%, the ICER is approximately £8,000 per QALY. At admission rates of greater than 42%, expectant management is dominated by immediate birth.

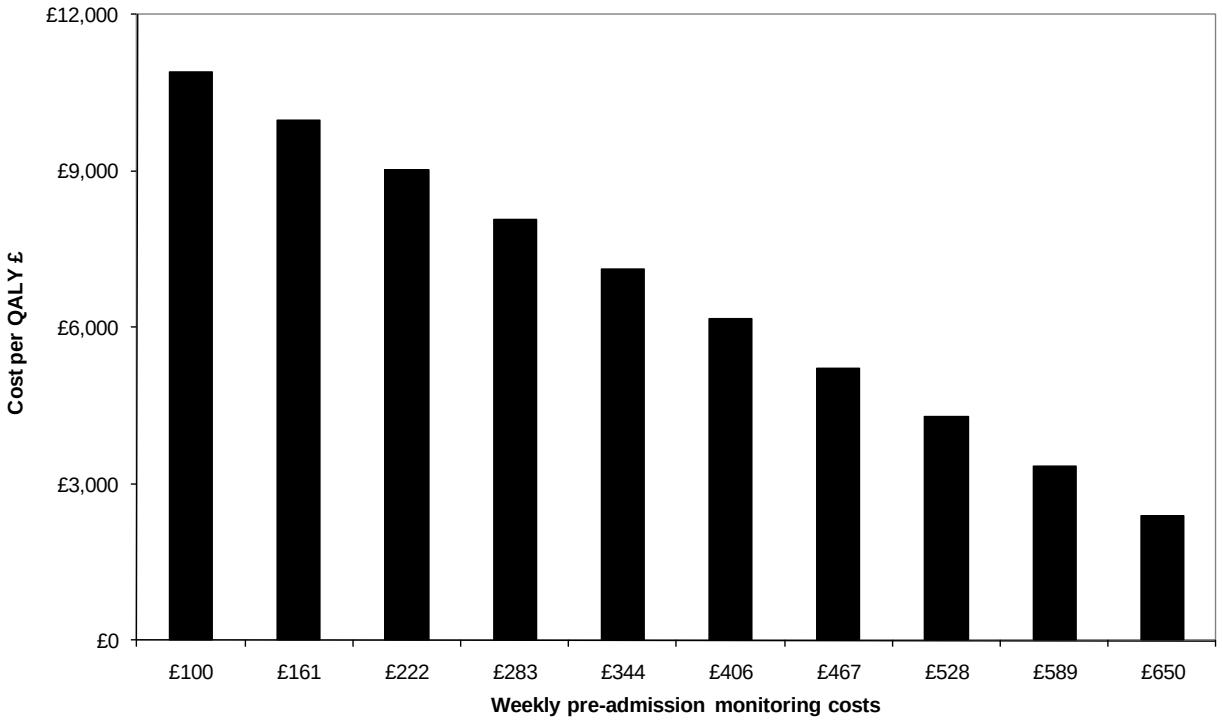

Figure J.4 Sensitivity analysis showing ICERs of immediate birth compared with expectant management in women with mild/moderate pre-eclampsia preterm, varying the pre-admission monitoring costs in the expectant management strategy

Varying the NICU costs

In the base model, the NICU costs were taken from the NHS reference costs[240] and were £1,423 per day (2008/09 prices). In the model, severe disease was approximated by rate of cerebral palsy. Only those neonates who had cerebral palsy were admitted into NICU. The costs of NICU stay were varied between £1,000 and £5,000 per day. This result shows that the model is not sensitive to changes in assumptions about NICU admission costs.

Varying the short-term utility loss due to pregnancy

In the base model, the quality of life weights used were obtained from Sonnenberg *et al.*[243] Short-term utility loss was assumed to be about 0.03 over the 9 months. In this analysis, the health-related quality of life loss ('utility') was varied between 0.1 and 0 (see Figure J.5). With a loss of utility of 0.1, the ICER was approximately £3,400 per QALY. If it was assumed that there were no utility loss from pregnancy, the ICERs fell to £2,700 per QALY, suggesting that immediate birth is cost effective.

Varying the short-term utility loss due to development of severe maternal disease

In this analysis, the short-term utility loss due to the development of severe maternal disease was varied between 0.6 and 0.95. The ICER remained below £3,000 per QALY across this range, suggesting that the model results are not sensitive to changes in the quality of life assumptions surrounding development of severe maternal disease.

Discussion

The model demonstrated that the immediate birth strategy compared with the expectant management strategy in women with mild to moderate pre-eclampsia preterm is cost effective, with an estimated ICER of around £2,900/QALY. However, this finding is highly sensitive to the incidence of severe disease used in the model.

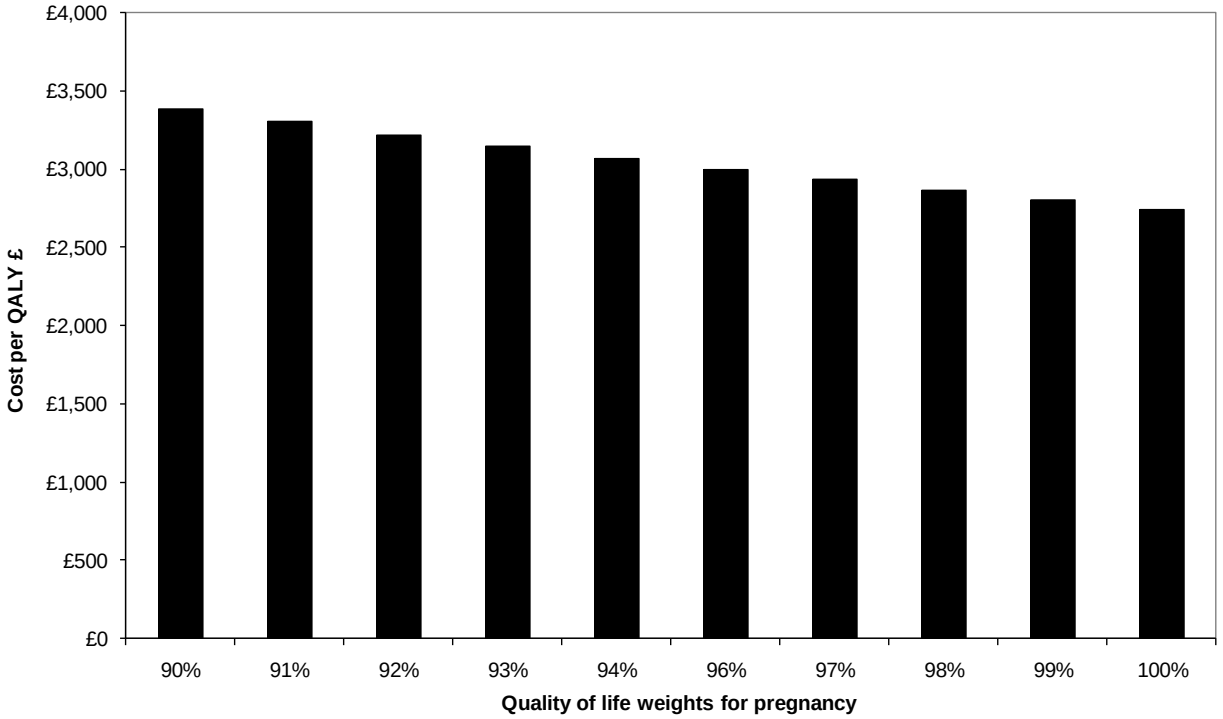

Figure J.5 Sensitivity analysis showing ICERs of immediate birth compared with expectant management in women with mild/moderate pre-eclampsia preterm, varying short-term utility loss due to pregnancy

The risk of developing severe disease is considerably higher in the expectant management group. The HYPITAT trial,[126] which compared the two strategies in women with gestational hypertension at term, demonstrated that severe disease was reduced by half when women with mild/moderate gestational hypertension were offered immediate birth. This could be an important finding as admission to HDU and ICU due to development of severe disease has significant cost implications and adversely affects the quality of life of the women.

Effectiveness data were taken from observational studies[145;192;242] and a Cochrane review comparing vaginal prostaglandins used for third-trimester cervical ripening or labour induction with placebo/no treatment in unselected pregnant women.[248] In the absence of published comparative data comparing the two policies, however, the GDG used expert judgement and observational data to populate the model. The GDG is aware of a continuing trial comparing immediate birth with expectant management in women with mild/moderate pre-eclampsia.

It is acknowledged that quality of life weightings (utility) data, derived from pregnant women without gestational hypertension and those hospitalised in ICU for any other reason, may not accurately approximate those for women who have pre-eclampsia with mild or moderate hypertension. However, given the lack of published quality of life data in women with pre-eclampsia, the GDG felt that this was the best estimate available for the quality of life for women with pre-eclampsia. Sensitivity analysis using different quality of life weights did not alter the cost-effectiveness outcome.

Conclusion

The model shows that the immediate birth strategy is cost effective compared with the expectant management strategy in women who have pre-eclampsia with mild or moderate hypertension at 34–37 weeks of gestation. However, the results need to be interpreted with caution in the absence of head-to-head trials comparing the two alternatives.

Appendix K

Cost effectiveness of using a 1+ dipstick urinalysis threshold versus a 2+ dipstick urinalysis threshold in screening for proteinuria in women with gestational hypertension

Introduction

The detection of proteinuria is important in the management of hypertensive pregnancies. The presence of proteinuria is often a requirement for a diagnosis of pre-eclampsia and, because the risk of birth complications increases with nephrotic-range proteinuria, the quantification of proteinuria is also important.

A dipstick urinalysis (using reagent strips) is usually the first stage in the detection of proteinuria. The reagent strips are used to grade urine protein concentration as nil, trace, 1+ (0.3 g/litre), 2+ (1 g/litre) or 3+ (≥ 3 g/litre). Current practice in the UK (GDG opinion) is to use 1+ as the basis for predicting 300 mg/24 hour proteinuria, which is tested in dipstick-positive patients with a 24-hour urine collection (the gold standard).

However, there is uncertainty about whether 1+ represents the optimal threshold that should be used for a positive test result.[80] Using a higher threshold increases the positive predictive value and reduces the number of 24-hour urine collections undertaken. However, it also results in more missed cases. * An economic evaluation was thus undertaken to compare the cost effectiveness of using a 1+ threshold versus a 2+ threshold in pregnant women with new-onset mild to moderate gestational hypertension.

Economic evaluation and decision-making

Economic evaluation is a tool that analysts and decision-makers can use to compare competing options and select those that best meet their needs within budget constraints. Cost-effectiveness analysis helps to define the opportunity cost of selecting one intervention rather than another. Different options are compared by using comparable measures of cost and outcome, and the resulting incremental cost-effectiveness ratios (ICERs) can be used to determine the additional cost of each additional unit of health outcome. The standard health outcome measure for NICE cost-effectiveness analyses is the quality-adjusted life year (QALY) since it allows the costs and outcomes of different health programmes to be valued using the same units of effectiveness.

Where one option is cheaper and more effective, its cost effectiveness is unambiguous. Where there is a trade-off, the additional costs and additional health gain of moving from a lower cost intervention to a higher cost intervention are estimated. NICE has a nominal threshold of £20,000 per QALY, meaning that if a higher cost intervention costs less than £20,000 per additional QALY then it represents good value for money and should be funded by the NHS. This is a useful yardstick for decision-makers since it provides guidance on which interventions should and which should not be publicly funded.[38]

In diagnostics studies, effectiveness is often measured in terms of the diagnostic accuracy of the test rather than its impact on health gain. However, information on diagnostic accuracy alone cannot demonstrate the cost effectiveness of the test, which ultimately depends on

* Patients with disease who have a 1+ dipstick reading.

improvements in health based on treatment efficacy following diagnosis. Test accuracy does not tell us anything about the value of increasing the number of cases detected or reducing the number of cases missed, or how much you can improve health by more correct diagnosis. The lowest incremental cost per correct diagnosis may not necessarily be the lowest cost per health gain option and cannot be assumed to be so.

Methods

Central to this model is the trade-off between false negatives and false positives resulting from a change of diagnostic threshold, as would be represented by the receiver operating characteristics (ROC) of the test. The magnitude of the trade-off is captured by sensitivity and specificity of the test at various thresholds. A decision-analytic model was used to compare the incremental costs and effects of using either a 1+ or a 2+ dipstick threshold in the detection of proteinuria. A schematic representation of part of the model in shown in Figure K.1.

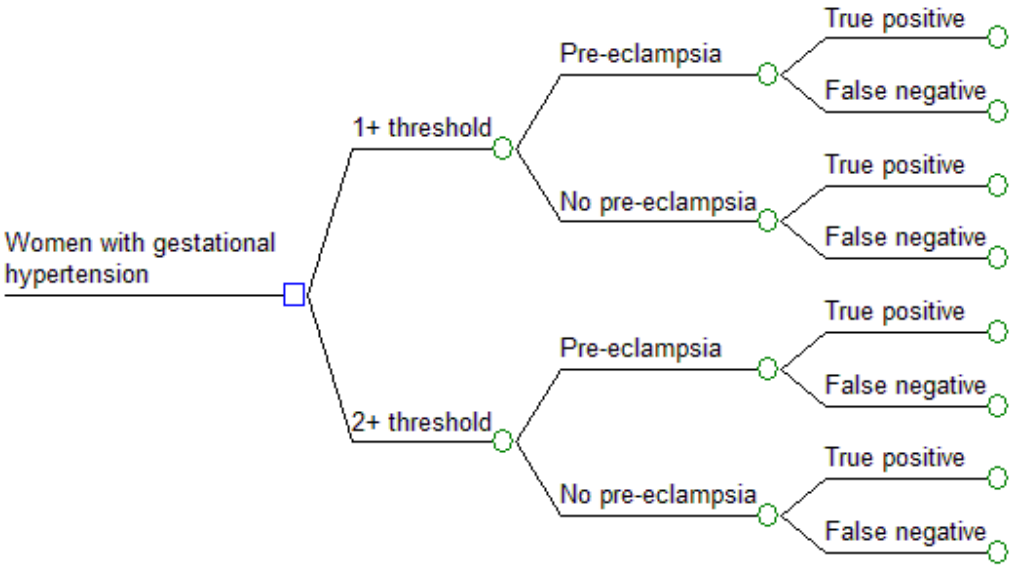

Figure K.1 Decision tree to compare the cost effectiveness of using a 1+ dipstick urinalysis threshold versus a 2+ dipstick urinalysis threshold in the detection and quantification of proteinuria in women with gestational hypertension.

Model structure and description

Test accuracy at the various thresholds determines the proportions of true positives and negatives and of false positives and negatives. True positives will have an enhanced care package while true negatives will require less care. False positives will incur an additional day of hospitalisation awaiting the confirmatory 24-hour urine tests (gold standard) and will eventually be managed as true negatives. False negatives will eventually be managed as true positives as it is assumed that their pre-eclampsia will be detected at a later date. It is also assumed that 10% of these false negatives progress to severe disease (eclampsia) as a consequence of their incorrect dipstick diagnosis.

True negatives and false positives follow the pathway of women with gestational hypertension, described in Appendix I (model for women with mild/moderate gestational hypertension). True positives and false negatives follow the pathway for women with pre-eclampsia, described in Appendix J (model for women with mild/moderate pre-eclampsia).

A systematic review of urinary dipstick testing pooled data from six studies to estimate the sensitivity and specificity of visual reading of dipsticks using a 1+ threshold only.[80] However, it

was not possible to use these pooled values in this model because the values were not logically consistent with the much more limited data available for the sensitivity and specificity of visual urinalysis at a 2+ threshold.* Instead, a single study that compared the sensitivity and specificity of visual urinalysis at both a 1+ and a 2+ threshold was used.[249] For consistency, a single study that compared a 1+ and a 2+ threshold was used to estimate sensitivities and specificities for automated urinalysis (automated reading of reagent strips).[83] The model test characteristics are indicated in Table K.1.

Table K.1 Model test characteristics

Diagnostic technology	Dipstick urinalysis cut-off point				Source
	1+ (0.3 g/litre)		2+ (1 g/litre)		
	Sensitivity	Specificity	Sensitivity	Specificity	
Visual urinalysis	86%	39%	64%	85%	Brown *et al.*[249]
Automated urinalysis	90%	86%	83%	98%	Saudan *et al.*[83]

Other parameters

Prevalence

A recent study on the predictive value of clinical and laboratory indices at first assessment in women referred with suspected gestational hypertension by Anumba *et al.*[97] found that the overall prevalence of pre-eclampsia in women with confirmed gestational hypertension was about 18%. This study also reported the the prevalence of pre-eclampsia in women with severe hypertension was about 34%. In the base-case analysis, a prevalence of 18% was assumed and then various ranges were tested in sensitivity analysis. Data on test accuracy and prevalence were combined to estimate the percentage of patients correctly diagnosed.

Clinical management

It was assumed that true negatives are managed as per the guideline recommendations for women with new-onset hypertension without proteinuria, dependent on whether they have mild or moderate hypertension. For false negatives, it was assumed that they would eventually be managed as true positives as their proteinuria would be detected at a later date. It was also assumed that 10% of true negatives would progress to severe disease (eclampsia) as a result of being initially misdiagnosed. Women without proteinuria are managed as outpatients (gestational hypertension protocol; see Table K.2).

Table K.2 Care plan for women with new-onset hypertension and no proteinuria (gestational hypertension)

Mild hypertension (< 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)
Do not routinely measure blood pressure more than once a week	Measure blood pressure at least twice a week
Test for the presence of proteinuria at each visit	Test for the presence of proteinuria at each visit
Do not carry out any blood tests	Test urea electrolytes and request a full blood count. Do not carry out further blood test if no proteinuria at subsequent visits

It was assumed that true positives are managed as per the guideline recommendations for women with new-onset hypertension with proteinuria depending on whether they have mild or moderate hypertension. Women with a false positive result are hospitalised for a day and

* Consistency here requires that sensitivity decreases as a function of using a higher cut-off (1+ patients with disease are missed by using 2+ as a threshold) and that specificity increases (1+ patients without disease are no longer incorrectly diagnosed). The mean sensitivity of the pooled data for a 1+ threshold has a lower sensitivity than the more limited published data for a 2+ threshold. This is not necessarily surprising, given the wide range of sensitivities in the pooled analysis (mean 55%; 95% CI 37% to 72%). Furthermore, the data in the pooled analysis suggest that a trade-off between sensitivity and specificity exists, perhaps as a result of observer variability for example, even using the same 1+ threshold. In other words the studies with relatively low sensitivities had relatively high specificities and vice versa.

discharged once the confirmatory 24-hour urine tests are known. Subsequently, they are managed as per protocols for women with gestational hypertension without proteinuria. For women who have pre-eclampsia with mild hypertension, it was assumed that they would be hospitalised for a day while those with moderate pre-eclampsia would be hospitalised for 4 days (pre-eclampsia protocol; see Table K.3).

Table K.3 Care plan for women with new-onset hypertension and significant proteinuria (pre-eclampsia)

Mild hypertension (< 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)
Admit to hospital for evaluation and treatment	Admit to hospital for evaluation and treatment.
Measure blood pressure at least four times a day	Measure blood pressure at least four times a day
Monitor using the following tests twice a week: • full blood count • platelets • serum creatinine • transaminase • bilirubin	Monitor using the following tests three times a week: • full blood count • platelets • serum creatinine • transaminase • bilirubin
Do not repeat quantification of proteinuria	Do not repeat quantification of proteinuria

Cost parameters

The purchase of medical equipment (an automated reagent-strip reading device in this case) carries an opportunity cost that differs from operating costs such as labour and consumables in certain respects. The purchase of the readers involves an upfront payment before use. However, that cost is fixed as it does not vary with the number of diagnoses undertaken. The equipment can be used over a number of years before it needs to be replaced. Equipment costs have two facets:

- *opportunity cost* – the money spent on the equipment could have been invested in some other venture yielding positive benefits; this is calculated by applying an interest rate to the sum invested in the equipment
- *depreciation cost* – the equipment has a certain lifespan and depreciates over time; eventually, the equipment has to be replaced.

In economic evaluation, the usual practice is to annuitise the initial capital outlay over the expected life of the equipment. This gives an 'equivalent annual cost', which can then be divided by the number of patients treated annually to assign a unit cost of using that equipment.

Calculating the equivalent annual cost means making an allowance for the differential timing of costs. This involves discounting. The formula for calculating the equivalent annual cost is given below:

$$E = \frac{K - S/(1+r)^n}{A(n,r)}$$

where:

E = equivalent annual cost
K = purchase price of equipment
S = resale value
r = discount (interest rate)
n = equipment lifespan
$A(n,r)$ = annuity factor (n years at interest rate r)

The cost of an automated reagent-strip reading device was assumed to be £740 (£400 to £1,000). We assumed the automated reagent-strip reading device would last for 5 years and 100 women would use it per year, thus over the 5 years 500 women would use the machine. The automated reagent-strip reading device is assumed to have no resale value and an annual discount rate of 3.5% has been used.[38] This gives a cost per test of £1.64.

This and other cost parameters used in the model are shown in Table K.4.

Table K.4 Health service costs incurred by women who have pre-eclampsia with mild or moderate hypertension, 2008–09

Resource items	Value	Source
Cost of managing gestational hypertension (true negative)	£2,774	Calculated in Appendix I, as the cost per women with gestational hypertension[a]
Cost of managing gestational hypertension (false positive)	£2,949	Calculated in Appendix I, as the cost per women with gestational hypertension plus an additional day of hospitalisation[a]
Cost of managing pre-eclampsia (true positive)	£4,300	Calculated in Appendix J, as the cost per women with pre-eclampsia
Cost of severe pre-eclampsia (following false negatives)	£5,700	GDG[b] (it is assumed that 10% of false negatives progress to severe pre-eclampsia with the remainder managed as true positives)
Cost per test of automated reagent-strip reading device	£1.64	GDG

[a] The costs (values) shown are for women with moderate gestational hypertension. For women with mild gestational hypertension the costs would be half those shown.

[b] 90% of women would need ceasarean section, 5% uncomplicated vaginal birth and 5% assisted vaginal birth. 50% will develop severe pre-eclampsia /eclampsia and 5% of these go to the intensive care unit while 95% go to the high-dependency unit.

Estimation of QALY loss for false negatives

It is assumed that a neonatal death carries a loss of 27.7 QALYs. This is based on a life expectancy of 80 years (the average of male and female life expectancies at birth[250] lived in perfect health and discounted at a rate of 3.5% per year[38]). For pregnant women, it was assumed that the age at birth was 29 years[251] and that remaining life expectancy was 53 years.[250] Assuming this is lived in 'normal' health implies that a maternal death results in a loss of 24.8 discounted QALYs. The 24.8 discounted QALYs is the upper overestimate of the value of a maternal life saved. Same with neonatal death averted, i.e. it is an overestimate which overall makes the intervention appear more cost effective.

We used data on maternal and neonatal mortality for women with pre-eclampsia (representing true positives) and data on women with severe pre-eclampsia or eclampsia to estimate the weighted QALY loss from missed cases (Table K.5).

Table K.5 Maternal and neonatal mortality in pre-eclampsia and severe pre-eclampsia/eclampsia

Severity	Outcome	Value	Source
Pre-eclampsia	Neonatal death	0.56%	CEMACH[241]
	Maternal death	0.79%	Erogul[252]
Severe pre-eclampsia or eclampsia	Neonatal death	5.6%	Douglas[253]
	Maternal death	0.9%	Erogul[252] (midpoint of range)

Therefore the estimated QALY loss from a false negative, relative to a true positive, is given by the following:

QALY loss is calculated as the proportion of false negative women assumed to progress to severe disease (0.10) multiplied by the summation of maternal and neonatal QALY loss. Maternal and neonatal QALY loss were derived from the difference in mortality between pre-eclampsia and severe pre-eclampsia multiplied by discounted life expectancy as shown in the formula below.

$$\text{QALY loss} = 0.10 \times ([\{0.056 - 0.0056\} \times 27.7] + [\{0.009 - 0.0079\} \times 24.8]) = 0.14$$

Sensitivity analysis

One-way sensitivity analysis was undertaken on the prevalence of pre-eclampsia and on the probability of a woman with a false negative test result progressing to severe disease. This would indicate to what extent the base-case conclusion held under less favourable scenarios. These parameters were chosen because of the impact they may have on trade-offs at different thresholds and the implication of these trade-offs in terms of final outcomes, that is, the consequences of changing the rate of false negatives (missed cases) and false positives (overtreatment) in the tested population. Since there is a considerable amount of uncertainty with regard to the diagnostic accuracy of the tests, a two-way analysis was undertaken to explore whether different values for test accuracy (from the current best estimate) changed the order of cost effectiveness in the model. Owing to time and data limitations, it was not possible to perform a probabilistic sensitivity analysis, which would have provided a better understanding of the uncertainty surrounding the test accuracy data.

Results

The results are based on a cohort of 60 000 women, which is approximately the number of pregnancies per year in England and Wales with gestational hypertension.

Visual urinalysis and automated urinalysis

Tables K.6 and K.8 show the implications in terms of correct diagnoses in moving from a 1+ threshold to a 2+ threshold for visual and automated urinalysis, respectively. In moving to a 2+ threshold, the reduction in false positive diagnoses comes with a trade-off involving more missed cases. Tables K.7 and K.9 show the cost-effectiveness implications of this trade-off for visual and automated urinalysis, respectively. The reduction in false positives using a 2+ threshold does reduce costs but at a QALY loss because of the increase in missed cases. In both cases, the incremental cost effectiveness of 1+ relative to 2+ is less than £20,000 per QALY.

Table K.6 Diagnostic outcomes of 1+ threshold compared with 2+ threshold for visual urinalysis in a cohort of 60 000 women with gestational hypertension

Diagnostic outcome	1+	2+
True positive	9 288	6 912
False positive	30 012	7 380
False negative	1 512	3 888
True negative	19 188	41 820

Table K.7 Cost effectiveness of 1+ threshold compared with 2+ threshold for visual urinalysis in a cohort of 60 000 women with gestational hypertension

Threshold	Cost	QALY loss	Incremental cost	Incremental QALY	ICER
1+	£188,482,980	214	£3,627,960	337	£10,767
2+	£184,855,020	551			Not cost effective

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table K.8 Diagnostic outcomes of 1+ threshold compared with 2+ threshold for automated urinalysis in a cohort of 60 000 women with gestational hypertension

Diagnostic outcome	1+	2+
True positive	9 720	8 964
False positive	6 888	984
False negative	1 080	1 836
True negative	42 312	48 216

Table K.9 Cost effectiveness of 1+ threshold compared with 2+ threshold for automated urinalysis in a cohort of 60 000 women with gestational hypertension

Threshold	Cost	QALY loss	Incremental cost	Incremental QALY	ICER
1+	£184,375,800	153	£927,360	107	£8,650
2+	£183,448,440	260			Not cost effective

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Sensitivity analysis

Prevalence of pre-eclampsia

For visual urinalysis, the 1+ threshold remains the cost-effective option provided that the prevalence of pre-eclampsia is greater than 11%.

For automated urinalysis, the 1+ threshold remains cost effective where pre-eclampsia prevalence is greater than or equal to 9.2%. With lower pre-eclampsia prevalence than 9.2%, the ICER of 1+ exceeds £20,000 per QALY.

Proportion of false negatives proceeding to severe disease

A 1+ threshold is more cost effective than a 2+ threshold for visual urinalysis provided that at least 5.6% of false negatives would progress to severe disease as a result of their misdiagnosis.

The 1+ threshold is more cost effective than a 2+ threshold for automated urinalysis provided that the proportion of false negatives progressing to severe disease is 4.6% or greater.

Varying the increase in specificity and the reduction in sensitivity as a result of using a 2+ threshold instead of a 1+ threshold

The effect of varying the trade-off between an increase in false negatives and a reduction in false positives by moving to a 2+ threshold is shown in Figure K.2. The orange and red shaded regions show where a 1+ threshold would be cost effective relative to a 2+ threshold. The blue region represents a trade-off where there is only a small increase in missed cases but a relatively large reduction in false positives. Here the cost effectiveness of 1+ relative to 2+ exceeds £20,000 per QALY as the QALY gain from fewer missed cased is relatively small while there are significant additional costs from unnecessary testing in those subsequently found not to have pre-eclampsia.

Discussion

The base-case result suggests that using a 1+ threshold in urinalysis for the prediction of proteinuria is more cost effective than a 2+ threshold for women with new-onset mild to moderate gestational hypertension. This was true for both visual and automated urinalysis. In the visual urinalysis, the use of a 2+ threshold leads to a 22 percentage point fall in sensitivity with an offsetting 46 percentage point increase in specificity. For automated urinalysis, the corresponding fall in sensitivity and increase in specificity is 7 percentage points and 12 percentage points, respectively. As can be seen from Figure K.2, these changes in diagnostic accuracy fall within the orange region. In both cases, the increased QALY gain from the lower number of missed cases using 1+ is considered a good value for money even though overall costs are increased because of the higher number of false positives.

One-way sensitivity analysis suggested that a 1+ threshold would be more cost effective than a 2+ threshold even if the prevalence of pre-eclampsia and the probability of missed pre-eclampsia cases progressing to severe disease are considerably lower than is assumed in the base-case analysis. However, the published evidence comparing the use of 1+ and 2+ thresholds is quite limited and further research could give more reliable estimates of the trade-off resulting from different thresholds.

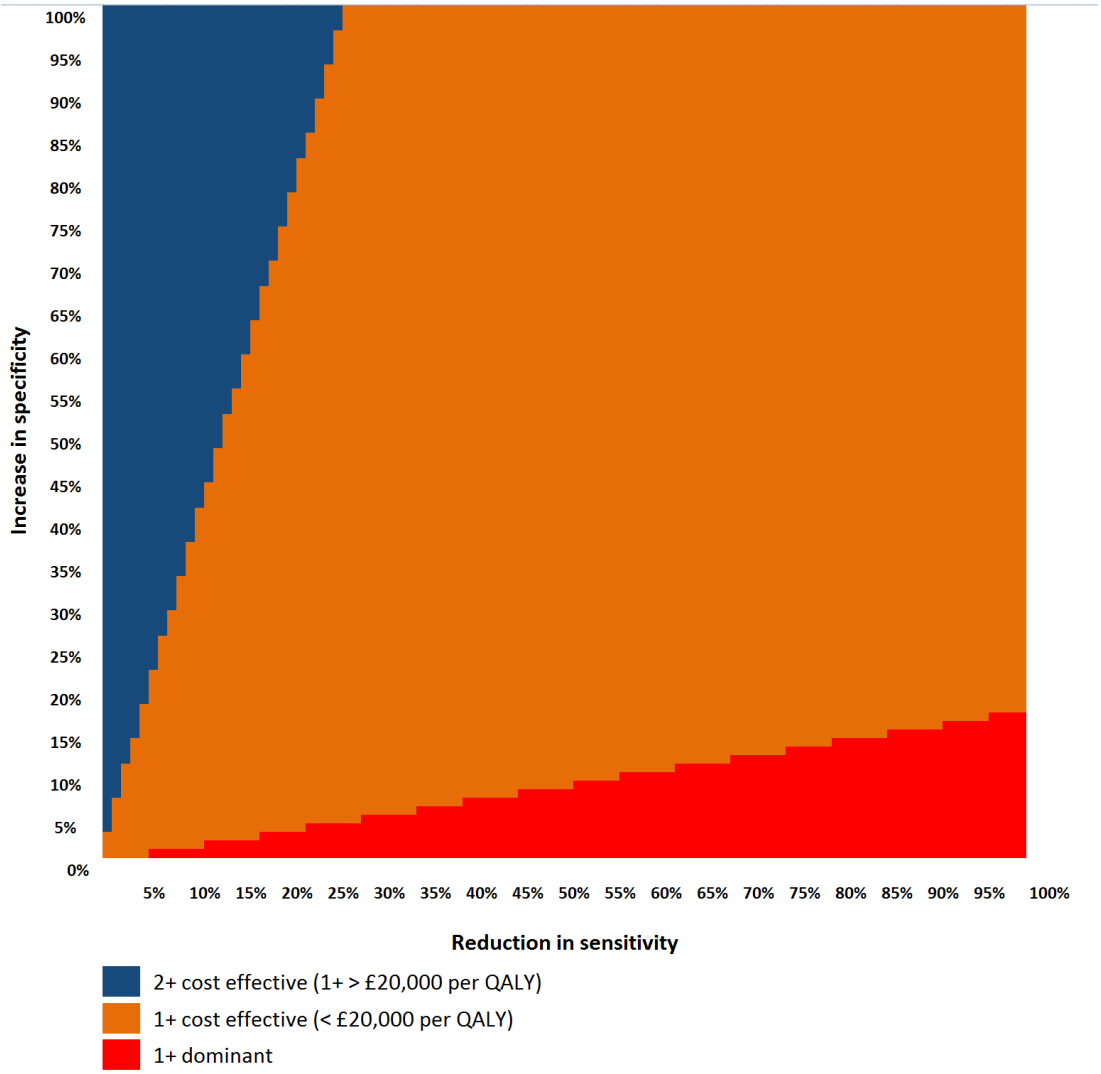

Figure K.2 Cost effectiveness of a 1+ dipstick threshold versus 2+ dipstick threshold for all hypothetical ROC curve trade-offs in moving from 1+ to 2+. The percentages on the horizontal and vertical axes represent a percentage point change from the 1+ threshold sensitivity and specificity. The diagram shows all theoretical combinations, which therefore includes a base-case sensitivity of 100% and specificity of 0%. However, not all of these combinations are practically feasible as sensitivity is always found to be < 100% and specificity > 0% when a 1+ threshold has been evaluated. Specificity, for example, can never increase by the full amount shown on the vertical axis by moving to 2+ because the specificity at 1+ is found to be considerably higher than 0%.

Conclusion

The evidence presented here suggests that current practice in the NHS of using a 1+ dipstick urinalysis threshold for the detection of proteinuria may be more cost effective than using a 2+ dipstick urinalysis threshold. Therefore, in Appendix L which compares the cost effectiveness of visual urinalysis with automated urinalysis, a 1+ threshold is used.

Appendix L

Cost effectiveness of automated urinalysis compared with visual urinalysis in screening for proteinuria in women with gestational hypertension

Introduction

Detecting proteinuria in pregnant women is traditionally performed by routine visual reagent-strip (dipstick) urinalysis. The test strips are used to grade urine protein concentration as nil, trace, 1+ (0.3 g/litre), 2+ (1 g/litre) or 3+ (≥3 g/litre). The GDG's view is that current practice in the UK is to use 1+ (approximating to 300mg/24 hour proteinuria in a 24-hour urine collection (the gold standard) in women suspected of having pre-eclampsia). The presence of proteinuria and its quantity increases the risk of pre-eclamptic complications. Recent studies have documented inaccuracies in this method, giving high false positive[83] and false negative results[81] when compared with the gold standard of 24-hour urine measurement. Clinically, a false positive test implies enhanced care for women who do not need it. Thus from an economic standpoint, over-diagnosis becomes an issue since women may be unnecessarily hospitalised and managed aggressively, using scarce NHS resources that could be better used elsewhere. False negative results mean women who should receive enhanced management are missed, with associated higher risks during birth.

Studies have shown that automated urinalysis (using an automated reagent-strip reading device) can improve the predictive power of urinalysis and eliminate the inter- and intra-observer variability that is present when visual dipstick urinalysis is used.[83] However, the cost effectiveness of automated urinalysis has not been evaluated. Practice is varied within the NHS, with the GDG estimating, based on an Action on Pre-Eclampsia survey, that approximately 20% of day assessment units currently use an automated reagent-strip reading device. The GDG requested a *de novo* model to establish the cost effectiveness of automated urinalysis compared with visual urinalysis.

Aim

To determine the cost effectiveness of automated urinalysis compared with routine visual urinalysis in the detection and quantification of proteinuria in pregnant women with new-onset mild to moderate gestational hypertension.

Methods

Development of the economic model

The systematic reviews of the accuracy of the automated urinalysis and the visual dipstick urinalysis undertaken for this guideline were the source of the sensitivity and specificity model parameters. The test performance was determined for various levels of protein concentration, which were classified as nil/trace for a negative dipstick test result, and 1+ (0.3 g/litre), 2+ (1 g/litre) or 3+ (> 3 g/litre) for a positive dipstick test result. The test performance was assumed to be the same for women with mild hypertension or moderate hypertension.

Test parameters

The test parameters are shown in Table L.1. For the sensitivity and specificity of automated urinalysis, data from the systematic review by Waugh *et al.*[80] were used. In a meta-analysis of six studies, the systematic review authors reported that, using a threshold of 1+, visual reading of dipsticks had sensitivity of 55% and specificity of 84%. A prospective diagnostic study undertaken in the UK compared visual and automated urinalysis head to head.[81] The visual dipstick urinalysis had a sensitivity of 51% (95% CI 39% to 62%) and a specificity of 78% (95% CI 68% to 86%), and was included in the meta-analysis of 1+ data. The automated reagent-strip reading device (Multistix® 8SG read using a Clinitek® 50 urine chemistry analyser) had a sensitivity of 82% (95% CI 71% to 90%) and specificity of 81% (95% CI 71% to 88%) and was used for the test accuracy parameters in this model.

Table L.1 Test performance data for urinalysis in the economic model using a 1+ (0.3 g/litre) threshold for women with mild to moderate gestational hypertension; data from Waugh *et al.*[80]

Test	Sensitivity	Specificity
Automated 1+ (0.3 g/litre)	82%	81%
Visual 1+ (0.3 g/litre)	55%	84%

For the cost assumptions, clinical management, prevalence and quality of life assumptions used in this model, refer to the Methods section of appendix K.

Sensitivity analysis

One-way sensitivity analysis was undertaken on the prevalence of pre-eclampsia, the cost of inpatient admission and the cost of the automated reagent-strip reading device. Ranges for parameter values changed in the one-way sensitivity analysis were chosen to favour visual urinalysis. This would indicate to what extent the base-case conclusion held under less favourable scenarios. Since there was a considerable amount of uncertainty with regard to the diagnostic accuracy of the tests, various hypothetical movements along the receiver operating characteristic (ROC) curve were explored to assess the thresholds for cost effectiveness using a 1+ or a 2+ threshold. Owing to time and data limitations, it was not possible to perform a probabilistic sensitivity analysis, which would have provided a better understanding of the uncertainty surrounding the test accuracy data.

Results

The diagnostic outcomes of using automated urinalysis versus visual urinalysis are shown in Table L.2 for a cohort of 60 000 pregnancies with gestational hypertension.

Table L.2 Diagnostic outcomes of automated urinalysis versus visual urinalysis for 60 000 women with mild to moderate gestational hypertension

	Visual	Automated
True positives	5940	8856
False positives	7872	9348
False negatives	4860	1944
True negatives	41 328	39 852
Negative predictive value	89.5%	95.3%
Positive predictive value	43.0%	48.6%

The base-case analysis suggested that automated urinalysis dominated visual urinalysis for both moderate and mild disease (see Tables L.3 and L.4).

Table L.3 Cost effectiveness of automated urinalysis compared with visual urinalysis using a 1+ (0.3 g/litre) threshold in 60 000 women with moderate gestational hypertension

Test	Cost	QALY loss	Incremental cost	Incremental QALY gain	ICER
Visual	£184,978,800	692	£51,540		Dominated
Automated	£184,927,260	277		415	Dominant

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Table L.4 Cost effectiveness of automated urinalysis compared with visual urinalysis using a 1+ (0.3 g/litre) threshold in 60 000 women with mild gestational hypertension

Test	Cost	QALY loss due to false negatives	Incremental cost	Incremental QALY gain	ICER
Visual	£92,489,400	692			
Automated	£92,512,830	277	£23,430	415	£56

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Sensitivity analysis

Varying the prevalence of pre-eclampsia

The prevalence of pre-eclampsia was varied between 1% and 20%. Figure L.1 shows that automated urinalysis in pregnant women with gestational hypertension is cost effective compared with visual urinalysis for all prevalence values in this range.

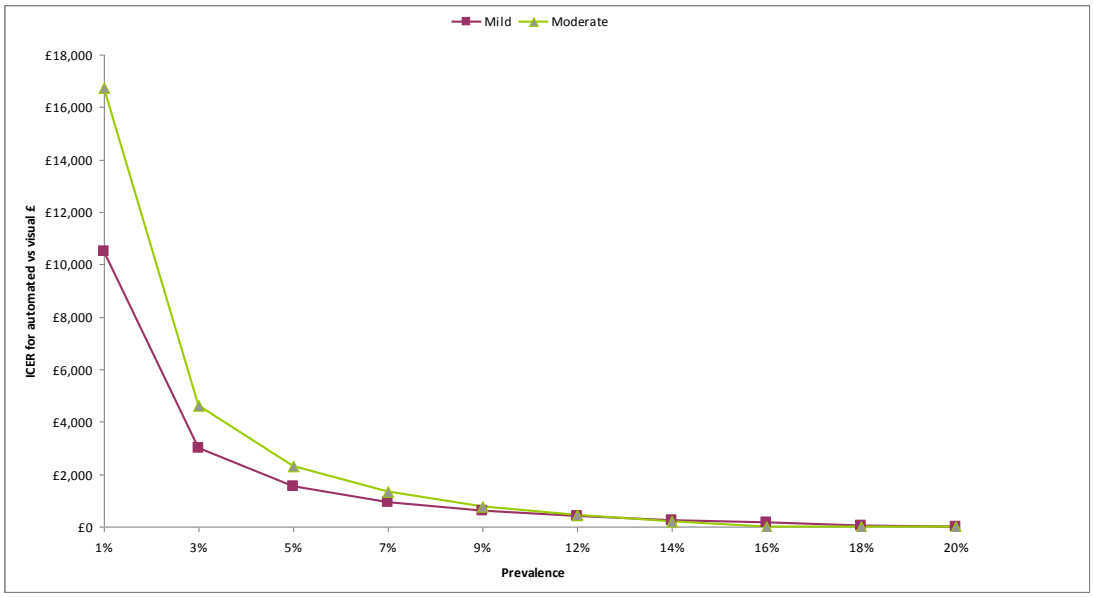

Figure L.1 ICER for automated urinalysis compared with visual urinalysis, varying the prevalence of pre-eclampsia in women with mild to moderate gestational hypertension

Varying the cost of inpatient admission

Inpatient costs are a function of the false positive rate. If a higher inpatient cost is assumed than in the base case, then this will favour visual urinalysis since it has a lower false positive rate. Therefore, inpatient costs were varied between £150 and £1000. The model results were not sensitive to changes in inpatient admission costs as automated urinalysis remained cost effective across the range that was tested. The ICERs remained below £3,000/QALY even when the worse case of £1,000 per day was assumed, as shown in Figure L.2.

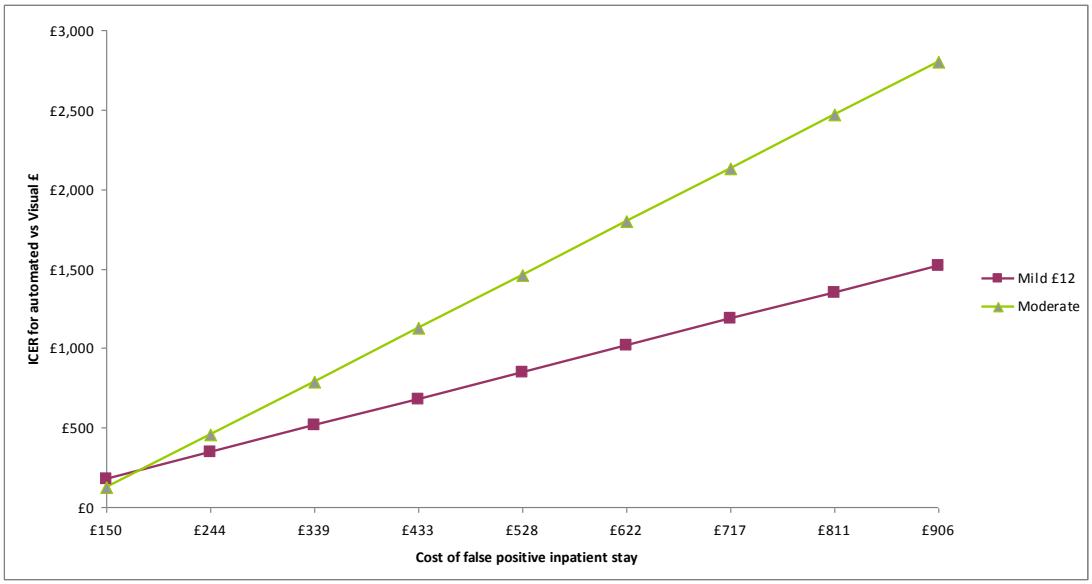

Figure L.2 ICER for automated urinalysis compared with visual urinalysis, varying the in-hospital cost in women with mild to moderate gestational hypertension

Varying the cost per test of the automated reagent-strip reading device

In the base-case analysis, automated urinalysis was dominant if the automated reagent-strip reading device cost per test was £1.64. Lower test costs would strengthen this dominant result. Therefore the impact of using higher costs per test was explored, using a range of £2 to £60, as shown in Figure L.3. At an automated reagent-strip reading device cost per test of £60, the ICER for both mild and moderate gestational hypertension would be approximately £8,500 per QALY. Such a high cost per test is unlikely as it would require that only three women per centre are tested annually using the device.

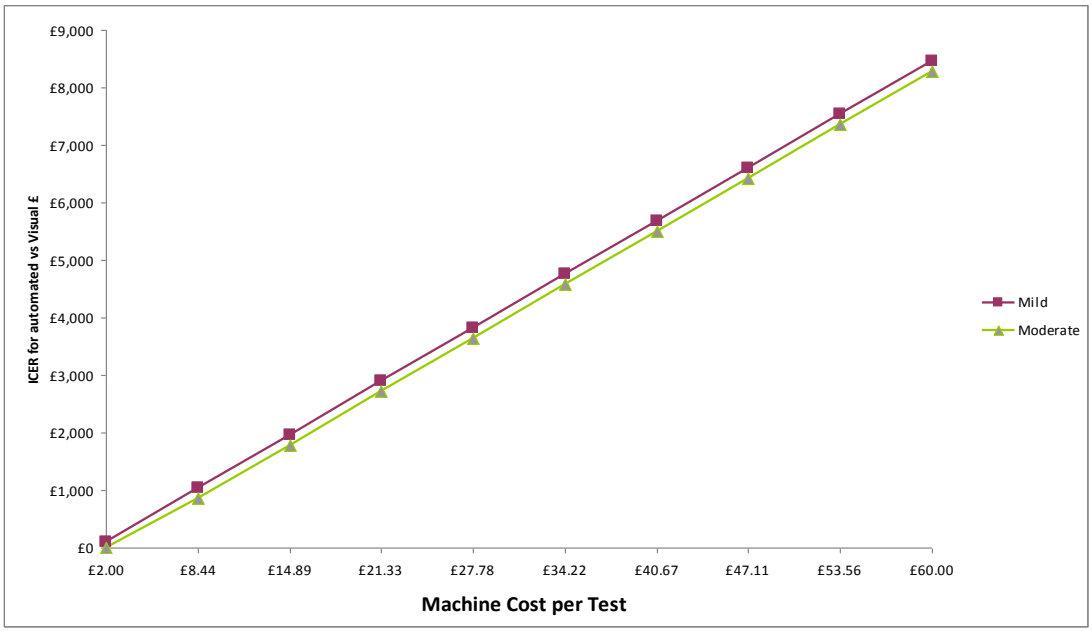

Figure L.3 ICER for automated urinalysis compared with visual urinalysis, varying the cost per test of the automated reagent-strip reading device in women with mild to moderate gestational hypertension

Varying the sensitivity and specificity of visual urinalysis (two-way analysis)

The test sensitivity and specificity were varied between all possible pairwise combinations between 50% and 100%, holding the test sensitivity and specificity of automated urinalysis constant at their base-case values. Figure L.4 is divided into four quadrants (A–D). The x-axis and y-axis represent sensitivity and specificity, respectively. The vertical and horizontal black lines represent the sensitivity and specificity of automated urinalysis. The two-way sensitivity analysis showed that all the individual point estimates of visual urinalysis fall outside the cost-effective regions compared with the best estimate of automated urinalysis.

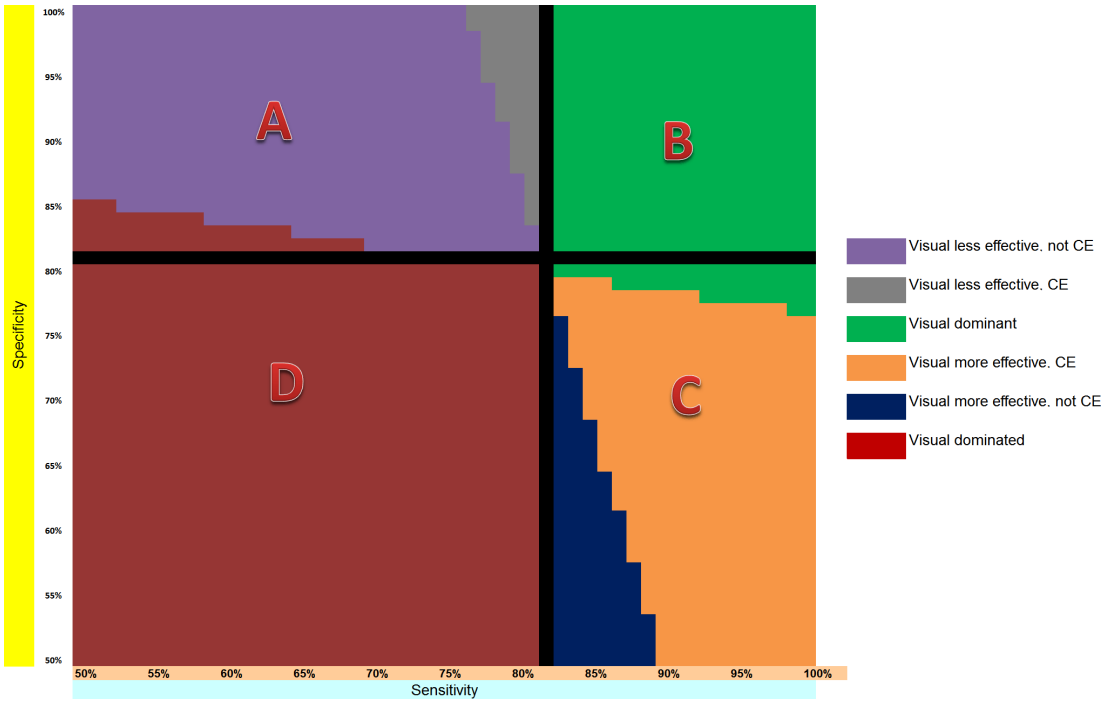

Figure L.4 Representation of the cost effectiveness of automated urinalysis compared with visual urinalysis, varying sensitivity and specificity of visual urinalysis (two-way analysis) assuming 10% of false negatives will progress to severe disease in women with mild to moderate gestational hypertension; the thick parallel black lines denote the sensitivity and specificity of automated urinalysis, which is kept constant

In quadrant A, the sensitivity of the automated urinalysis is always greater than or equal to the sensitivity of visual urinalysis. Also, the specificity of visual urinalysis is always greater than or equal to the specificity of automated urinalysis. In most of these scenarios, automated urinalysis is cost effective. However, there are cases when the visual urinalysis becomes cost effective, as shown by the grey region. This occurs when the sensitivity of visual urinalysis approaches that of automated urinalysis, resulting in a much lower difference in health outcomes, and when the higher specificity of visual urinalysis leads to cost savings by reducing further testing in women subsequently found not to have pre-eclampsia.

Quadrant B represents scenarios where the test characteristics of the visual urinalysis are all superior (better sensitivity and better specificity), resulting in dominance (visual urinalysis is both less expensive and more effective).

Quadrant C represents scenarios where the sensitivity of visual urinalysis is greater than or equal to the sensitivity of automated urinalysis and where the specificity of automated urinalysis is greater than or equal to the specificity of visual urinalysis. These scenarios are the opposite of those presented in the base case. The cost-effectiveness results in this region, not surprisingly, are the opposite of those of Quadrant A.

In Quadrant D, automated urinalysis has unambiguously better test characteristics with greater or equal sensitivity and specificity. In this quadrant, automated urinalysis dominates visual urinalysis.

Discussion

Using the most robust estimates for sensitivity and specificity in the published literature, the base-case analysis found that automated urinalysis is cost effective for women with mild hypertension with an estimated ICER of £56 per QALY. For women with moderate hypertension, automated urinalysis dominates visual urinalysis. Automated urinalysis remained cost effective for all of the one-way sensitivity analyses undertaken.

The two-way sensitivity analysis explored hypothetical scenarios in which automated urinalysis was no longer cost effective, by assuming, for example, that visual urinalysis had better sensitivity and specificity. However, the plausibility of the various scenarios needs to be taken into account. The individual studies that were included in the meta-analysis were considered on a case-by-case basis and it was found that automated urinalysis remained cost effective in all plausible scenarios, as was shown by the two-way sensitivity analysis reported in Figure L.4.

A limitation of the model was the way QALYs were estimated. Data on life expectancy from life tables were used and the life-time QALYs for neonates and their mothers were discounted assuming they lived the rest of their lives in perfect health. Clearly this would tend to give an over-estimation of the discounted lifetime QALY. However, given that most ill health occurs at the end of life, the simplifying assumption will have a relatively small impact on the overall discounted QALY. Furthermore, the estimate of QALY gain does not take into account morbidity, a bias that works in the opposite direction to the possible over-estimation of QALYs based on neonatal and maternal mortality.

Conclusion

If the base-case test characteristics of automated urinalysis are accepted as a reasonable approximation of their true accuracy then the sensitivity and specificity of visual urinalysis would have to be much higher than was reported in any of the studies included in the published meta-analysis[80] for it to be the preferred option. This much higher accuracy, therefore, does not seem plausible based on current published evidence. Published data on automated urinalysis are more limited and therefore its superior cost effectiveness to visual urinalysis cannot necessarily be assumed. However, based on the best currently available evidence, there are good reasons to suppose that automated urinalysis, a relatively low-cost technology, is more cost effective.

Appendix M

Cost effectiveness of quantifying proteinuria in women with gestational hypertension

Introduction

The GDG initially compared the cost effectiveness of automated reagent-strip reading devices (automated urinalysis) with visual reading of reagent strips (dipsticks; visual urinalysis). The analysis presented in Appendix L suggested that automated urinalysis was more cost effective than visual urinalysis, and that formed the basis of the initial guideline recommendations. Following the pre-publication check, there were suggestions that protein:creatinine ratio (PCR) should be included as a comparator. It was thus agreed to undertake an additional analysis in which the the following screening methods for proteinuria in women with mild or moderate gestational hypertension were compared:

- use of protein:creatinine ratio alone (PCR strategy)
- use of an automated reagent-strip reading device followed by protein:creatinine ratio in women with a positive test result on the automated reagent-strip reading device (Auto + PCR strategy)
- use of an automated reagent-strip reading device followed by a validated 24-hour urine collection in women with a positive test result on the automated reagent-strip reading device (Auto + 24-hour).

An automated reagent-strip reading device provides a point-of-care screening test, and a further gold standard test is needed to confirm the diagnosis. Traditionally, 24-hour urine collection has been regarded as the gold standard, but it has been suggested that PCR could fulfil this function. Thus, in the second and third strategies, PCR and 24-hour urine collection are considered to be the gold standard tests for quantifying proteinuria, respectively. However, PCR results can be available within a few hours and so the GDG also considered that PCR could be used directly in place of an initial screening test, in which case there would be no requirement for a confirmatory test.

The use of spot urinary PCR and spot urinary albumin:creatinine ratio (ACR) to estimate proteinuria is well established in the management of chronic kidney disease. More recently, it has started to be used in the management of hypertensive disorders during pregnancy, as in the case of the Australian and New Zealand guidelines on hypertension in pregnancy.[254] The GDG's view is that some tertiary centres in the UK use automated reagent-strip reading devices and PCR to screen for and quantify proteinuria.

Studies have shown that use of an automated reagent-strip reading device and PCR can improve the predictive power of urinalysis and eliminate the inter- and intra-observer variability that is present when visual dipstick urinalysis is used.[83] Leanos-Miranda *et al.*[91] suggested that PCR may be used as an alternative to 24-hour urine collection. However, the cost effectiveness of PCR alone, an automated reagent-strip reading device followed by PCR in women with a positive automated reagent-strip test result, or an automated reagent-strip reading device followed by 24-hour urine collection in women with a positive automated reagent-strip test result has not been evaluated. Practice varies within the NHS and the GDG estimates that approximately 20% of day assessment units use an automated reagent-strip reading device (based on a survey conducted by Action on Pre-Eclampsia) and that PCR is used in many centres (GDG opinion; PCR use was not evaluated in the Action on Pre-Eclampsia survey).

Aim

To determine the cost effectiveness of PCR alone, of an automated reagent-strip reading device followed by PCR in women with a positive automated reading device test result, and of an automated reagent-strip reading device followed by 24-hour urine collection in women with a positive automated reading device test result in screening for significant proteinuria in pregnant women with new-onset mild or moderate gestational hypertension.

Methods

Test parameters

The test parameters are shown in Table M.1. For the sensitivity and specificity of the automated reagent-strip reading device, we used data from the systematic review by Waugh *et al.*[81] Data for PCR were taken from the five studies that assessed the accuracy of spot PCR compared with 24-hour urine collection for the screening and quantification of significant proteinuria in hypertensive pregnant women.[90-94] The studies used different cut-off points and the five studies could not be meta-analysed owing to significant heterogeneity. Therefore, the results for each study were analysed separately.

Table M.1 Test accuracy statistics used in the health economic model for women with mild or moderate gestational hypertension

Test	Sensitivity (95% CI)	Specificity (95% CI)
PCR (Al *et al.*, 2004)[94]	80% (64% to 91%)	74% (66% to 81%)
PCR (Dwyer *et al.*, 2008)[90]	66% (52% to 78%)	95% (86% to 99%)
PCR (Leanos-Miranda *et al.*, 2007)[91]	98% (96% to 99%)	99% (98% to 99.5%)
PCR (Ramos *et al.*, 1999)[92]	94% (not reported)	80% (not reported)
PCR (Wheeler *et al.*, 2007) [93]	86.8% (not reported)	77.6% (not reported)
Automated reagent-strip reading device (Waugh *et al.*, 2005) [81]	82% (71% to 90%)	81% (71% to 88%)

Prevalence of pre-eclampsia

In the base-case analysis, a prevalence of 18% was assumed and various ranges were tested as part of sensitivity analysis (see Appendix K).

Clinical management

The clinical management of women in the model is described in Appendix K.

Cost parameters

The cost inputs used in the model are shown in Table M.2. It was assumed that any PCR false positives would be managed in the same way as true positives.

Estimation of QALY loss for false negatives

The estimation of QALY loss for false negatives is described in Appendix K.

Sensitivity analysis

Two-way sensitivity analysis was undertaken to assess the extent to which the results were affected by different test accuracy values.

Table M.2 Health service costs incurred by women who have pre-eclampsia with mild or moderate hypertension, 2008–09

Resource items	Value	Source	Notes
Managing gestational hypertension (true negative)	£2,774	See Table K.4	Calculated as the cost per women with gestational hypertension[a]
Managing gestational hypertension (false positive)	£2,949	See Table K.4	Calculated as the cost per women with gestational hypertension plus an additional day of hospitalisation[a]
Managing pre-eclampsia (true positive)	£4,300	See Table K.4	Calculated as the cost per women with pre-eclampsia
Severe pre-eclampsia (following false negatives)	£5,700	See Table K.4	At baseline, 10% of false negatives are presumed to progress to severe pre-eclampsia, with the remainder ultimately managed as true positives
Automated urinalysis	£3.13	GDG, Appendix K	Calculated as (cost of nurse/hour × 2 minutes of staff time to undertake test) + cost of Multistix® 8SG reagent strips + per-test cost of the automated reagent-strip reading device
Cost of PCR	£4.91		Calculated as (cost of staff nurse × staff time) + biochemistry + cost of phlebotomy
Per-test cost of automated reagent-strip reading device	£1.64	See Appendix K	Details of the calculation are described in Appendix K
Biochemical test	£1.34	NHS Reference Costs 2008/9[255]	
Staff cost per hour	£34.00	Curtis and Netten 2009[256]	
Multistix® 8SG reagent strips	£0.34	www.midmeds.co.uk/bayer-multistix-p-233.html	Calculated from cost of 100 strips at £34
Phlebotomy	£2.44	NHS Reference Costs 2008/9[255]	

[a] The costs (values) shown are for women with moderate gestational hypertension. For women with mild gestational hypertension the costs would be half those shown.

Results

Tables M.3 and M.4 give the diagnostic outcomes and costs, respectively, of the diagnostic strategies using a 'best-case' scenario for PCR. Equivalent data for a 'worst-case' scenario for PCR are presented in Tables M.5 and M.6.

Table M.3 Diagnostic outcomes of PCR versus an automated reagent-strip reading device for 60 000 women with mild or moderate gestational hypertension using Leanos-Miranda *et al.*[91]

Test result	PCR alone	Automated urinalysis followed by 24-hour urine collection	Automated urinalysis followed by PCR
True positives	10 562	8 856	8 661
False positives	443	0	84
False negatives	238	1 944	2 139
True negatives	48 757	49 200	49 116
Negative predictive value	99.5%	96.2%	95.8%
Positive predictive value	96.0%	100.0%	99.0%

Table M.4 Screening strategy costs for 60 000 pregnant women with mild or moderate hypertension using Leanos-Miranda *et al.*[91]

Strategy	Test cost	Treatment cost (mild)	Treatment cost (moderate)
PCR alone	£226,800	£91,814,888	£183,629,777
Automated urinalysis followed by PCR	£241,412	£93,189,330	£186,378,660
Automated urinalysis followed by 24- hour urine collection	£255,611	£93,267,161	£186,534,322

Table M.5 Diagnostic outcomes of PCR versus an automated reagent-strip reading device for 60 000 pregnant women with mild or moderate gestational hypertension using Dwyer *et al.*[90]

Test Result	PCR alone	Automated urinalysis followed by 24-hour urine collection	Automated urinalysis followed by PCR
True positives	7128	8856	5845
False positives	2460	0	467
False negatives	3672	1944	4955
True negatives	46740	49200	48733
Negative predictive value	92.7%	96.2%	90.8%
Positive predictive value	74.3%	100.0%	92.6%

Table M.6 Screening strategy costs for 60 000 pregnant women with mild or moderate hypertension using Dwyer *et al.*[90]

Strategy	Test cost	Treatment cost (mild)	Treatment cost (moderate)
PCR alone	£226,800	£93,594,520	£187,188,840
Automated urinalysis followed by PCR	£241,412	£93,189,330	£186,378,660
Automated urinalysis followed by 24-hour urine collection	£255,611	£93,756,729	£187,513,458

Summary cost-effectiveness results for all five studies are shown in Table M.7. The results suggest that PCR alone is the most cost-effective strategy using diagnostic accuracy data from Leonos-Miranda *et al.*[91] for both moderate and mild gestational hypertension. In this case, PCR alone is said to dominate the other strategies because it is both less costly and more effective (generating the highest QALY gain). It should be noted that the cost and QALY gain were calculated relative to no screening, where all cases of disease are modelled as false negatives. The other four analyses, based on smaller studies, indicated that using the automated reagent-strip reading device followed by 24-hour urine collection would be cost effective for women with mild or moderate hypertension.

Table M.7 Cost effectiveness of screening strategies in 60 000 pregnant women with mild or moderate gestational hypertension

Study	ICER (mild)	ICER (moderate)
Leanos-Miranda *et al.*, 2007[91]	PCR dominates	PCR dominates
Ramos *et al.*, 1999[92]	Auto + 24-hour: £967 per QALY	Auto + 24-hour: £1,742 per QALY
Wheeler *et al.*, 2007[93]	Auto + 24-hour: £967 per QALY	Auto + 24-hour: £1,742 per QALY
Al *et al.*, 2004[94]	Auto + 24-hour dominates	Auto + 24-hour dominates
Dwyer *et al.*, 2008[90]	Auto + 24-hour dominates	Auto + 24-hour dominates

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

Sensitivity analysis

As the results in Table M.7 show, the relative cost effectiveness of PCR alone versus using an automated reagent-strip reading device followed by a confirmatory 24-hour urine collection is highly dependent on the sensitivity and specificity of the tests. To further analyse the impact of test uncertainty, a two-way sensitivity analysis was undertaken in which the sensitivity and specificity of PCR were varied between all possible pairwise combinations between 50% and 100% while holding all other model parameters constant, including the sensitivity and specificity of the automated reagent-strip reading device, at their baseline values. The two-way sensitivity analysis was restricted to PCR alone because using the automated reagent-strip reading device followed by PCR was dominated in both the best- and worst-case scenarios for PCR.

Figure M.1 shows how cost effectiveness varied across different PCR test characteristics. The results presented are for 60 000 pregnant women with moderate gestational hypertension and the results for mild disease would be similar.

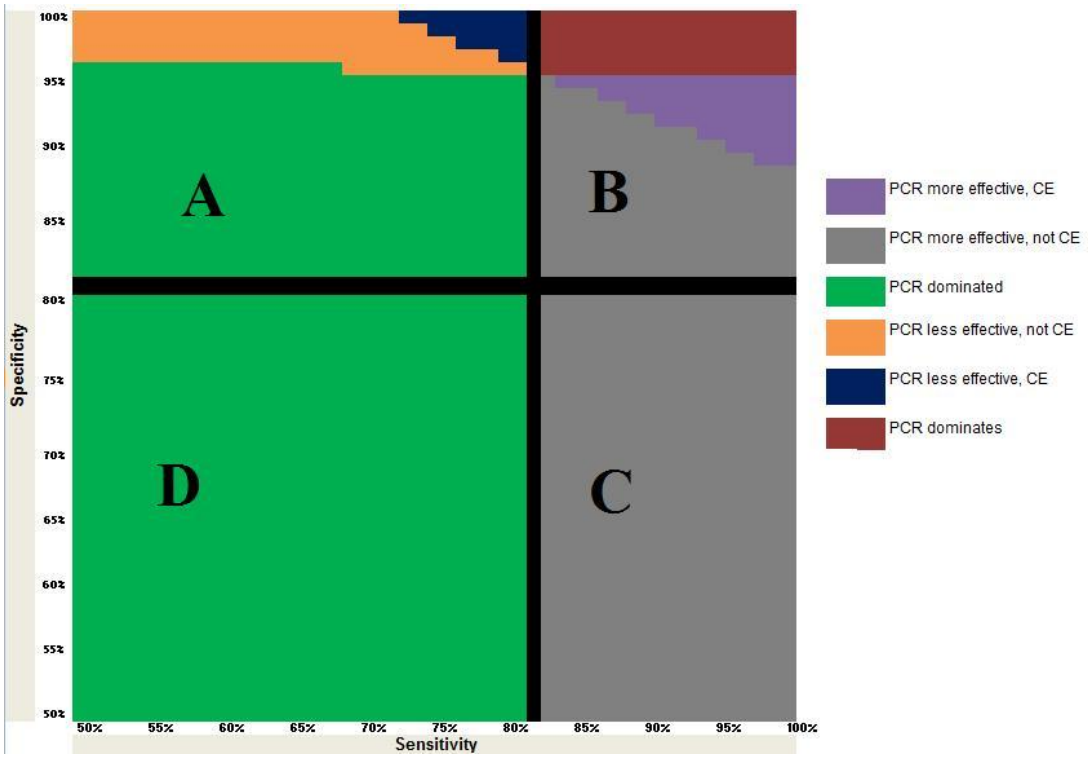

Figure M.1 Varying the sensitivity and specificity of PCR

Figure M.1 is divided into four quadrants (A–D). The *x*-axis and *y*-axis represent sensitivity and specificity, respectively. The vertical and horizontal black lines represent the sensitivity (82%) and specificity (81%) of the automated reagent-strip reading device.

In quadrant A, the sensitivity of PCR is always less than or equal to the sensitivity of automated urinalysis. Also, the specificity of PCR is always more than or equal to the specificity of the automated reagent-strip reading device. This quadrant shows that, unless the specificity of PCR is considerably better than that of the automated reagent-strip reading device, PCR alone is dominated. This is because lower sensitivity means that there are more false negatives resulting in a lower QALY gain and also because of high treatment costs associated with a greater number of false positives and false negatives. Although in this quadrant the automated reagent-strip reading device has a higher false positive rate, these are identified by the confirmatory 24-hour urine collection and this limits unnecessary treatment. As the specificity of PCR rises, the cost of false positives falls until a point is reached when PCR alone becomes the cheapest strategy.

However, even then, automated urinalysis would be preferred on cost-effectiveness grounds unless the sensitivity of PCR approaches that of the automated reagent-strip reading device.

Quadrant B represents scenarios where the test characteristics of PCR have better sensitivity and better specificity. In this quadrant, PCR alone will always produce the greater QALY gain as this is driven by test sensitivity. As in quadrant A, PCR may also have cost advantages at high specificities and this explains its dominant portion of this quadrant. As specificity falls, a point is reached where PCR alone becomes the more expensive strategy and in that case cost effectiveness is determined by whether the incremental QALY gain from PCR alone can be delivered at an acceptable incremental cost (i.e. at under £20,000 per QALY).

In Quadrant C, the lower specificity of PCR means that the incremental benefits arising from higher PCR sensitivity can never be justified by the incremental costs.

In Quadrant D, automated urinalysis has unambiguously better test characteristics with greater or equal sensitivity and specificity. In this quadrant, PCR is dominated because it has a lower QALY gain as a result of a lower sensitivity and a high cost of false positives and false negatives.

Discussion

The estimated sensitivities and specificities for PCR were obtained from five different studies that were not meta-analysed owing to heterogeneity. However, running the analysis for these studies separately showed that the cost-effectiveness results were sensitive to the accuracy of the respective tests. Where the most favourable PCR test accuracy data were used, PCR alone was shown to be the most cost-effective strategy, and this analysis was based on the largest of the five studies. However, when PCR sensitivity and specificity were derived from other studies, the use of an automated reagent-strip reading device followed by 24-hour urine collection was shown to be cost effective.

The use of an automated reagent-strip reading device followed by PCR is generally not cost effective, as shown by the best- and worst-case analyses. When PCR is assumed to have good test accuracy (the best case) then not only are there the additional diagnostic costs associated with sequential testing but there are higher treatment costs associated with missed cases (false negatives following automated urinalysis) in addition to QALY loss from those missed cases. When PCR is assumed to have a relatively low sensitivity (the worst case) then, comapared with using an automated reagent-strip reading device followed by 24-hour urine collection, more cases will be missed as some true positives with automated urinalysis will then be classified as negative (false negative) by the sequential PCR test. This is in addition to the false negatives following automated urinalysis. Therefore, using PCR as a confirmatory test will have a lower QALY gain than 24-hour urine collection, which would legitimately be considered the gold standard in this worst-case scenario. The conditions for the automated reagent-strip reading device followed by PCR to be cost effective require PCR to have much better test accuracy in women with a positive test result from the automated urinalysis than in the general population of pregnant women with hypertension and for there to be a large cost differential in favour of PCR relative to 24-hour urine collection.

A limitation of the model presented here is the way in which QALYs were estimated. Data on life expectancy from life tables were used and life-time QALYs for neonates and their mothers were discounted assuming they live the rest of their lives in perfect health. Clearly this will tend to over-estimate the discounted lifetime QALY. However, given that most ill health occurs at the end of life, this simplifying assumption will have a relatively small impact on the overall discounted QALY. Furthermore, the estimated QALY gain does not take account of morbidity, a bias that works in the opposite direction to the possible over-estimation of QALYs based on neonatal and maternal mortality.

Conclusion

The cost-effectiveness analysis suggests that the test with better sensitivity will often be the cost-effective option, although specificity can also be an important determinant, especially when test

sensitivities are similar. When the automated reagent-strip reading device has higher sensitivity and specificity than PCR, it dominates other options. Conversely, if the characteristics of PCR approach those of a gold standard test, as indicated by Leonos-Miranda *et al.*,[91] then PCR alone dominates.

Given the uncertainty about the differences in test accuracy, the GDG considered that using either PCR alone or an automated reagent-strip reading device followed by 24-hour collection were suitable for estimating proteinuria in a secondary care setting and could be justified on economic grounds. If an automated reagent-strip reading device were used for an initial test, then a 24-hour urine collection should be carried out for women with mild or moderate gestational hypertension and a reading of 1+ or more for proteinuria, based on economic grounds alone.

The GDG recognised that, from a practical point of view, PCR estimation is more convenient for the woman and healthcare professionals in that it provides a quicker result than 24-hour urine protein estimation.

Appendix N

Safety data for antihypertensives in pregnancy

Centrally acting drugs

Methyldopa (compatible) (Bm)

Crosses the placenta and achieves fetal concentrations similar to maternal serum concentration.

Collaborative Perinatal Project (CPP) – 1 infant exposure in 1st trimester – no abnormalities found.

Michigan Medicaid surveillance study – 242 infants exposed in 1st trimester – 11 (4.5%) major birth defects (10 expected). Does not support an association with methyldopa and congenital defects.

A decrease in intercranial volume has been reported after 1st trimester exposure to methyldopa. Children evaluated at 4 years of age showed no association between head size and retarded mental development.

A reduced systolic blood pressure of 4–5 mmHg in 24 infants for the first 2 days after delivery has been reported. This was not considered to be significant.

An infant born with oesophageal atresia with fistula, congenital heart disease, absent left kidney and hypospadias was exposed to methyldopa throughout pregnancy and clomiphene (in the 1st trimester).

Clonidine (Limited human data) (Cm)

No reports linking the use of clonidine with congenital defects or adverse fetal effects have been located. Clonidine has been used during all trimesters but experience in the 1st trimester is very limited.

Michigan Medicaid surveillance study – 59 infants exposed in 1st trimester – 3 (5.1%) major birth defects observed (3 expected). Number of exposures is too low to draw any conclusions.

Moxonidine

No information

Beta (β) blockers

Labetalol (Human data suggest low risk) (Cm)

Does not seem to pose a risk to the fetus, except possibly in the 1st trimester.

Michigan Medicaid surveillance study – 29 infants exposed in 1st trimester – 4 (13.8%) major birth defects (1 expected). May support an association with labetalol and congenital defects, but other factors (mother's disease, concurrent drug use and chance) may be involved.

No published reports of fetal malformations with labetalol exposure located, but experience in the 1st trimester is limited. Most reports found no adverse effects on birthweight, head circumference, Apgar scores or blood glucose control after in utero exposure.

One case of neonatal hypoglycaemia has been mentioned but mother was also taking a thiazide diuretic.

Offspring of mothers treated with labetalol had significantly higher birthweight compared with those exposed to atenolol (3280 g versus 2750 g).

A study comparing hospitalisation with or without labetalol showed significantly higher rates of growth retardation in labetalol exposed infants (19.1% versus 9.2%).

Fetal heart rate is apparently unaffected by labetalol in utero exposure. However, 2 studies have observed neonatal bradycardia in 5 infants (one case this was marked - < 100bpm - and persistent). Hypotension was also noted in another infant born at 28 weeks by caesarean section.

In a study examining the effects of labetalol exposure on term neonates, mild transient hypotension which resolved within 24 hours was reported (maternal dose – 100–300 mg TDS). Heart rate, respiratory rate, palmar sweating, blood glucose control and metabolic and vasomotor responses to cold stress did not differ between groups.

Several studies have shown a lack of effect of labetalol treatment on uterine contractions. One study reported a higher incidence of spontaneous labour in labetalol treated mothers (compared with methyldopa), however because most studies do not show this, the effect on uterine contractility is questionable.

Follow-up studies in children at 6 months of age to 10 infants exposed in utero showed normal growth and development.

Atenolol (Human data suggest risk in 2nd and 3rd trimesters) (Dm)

Crosses the placenta and achieves fetal concentrations similar to maternal serum concentration.

Michigan Medicaid surveillance study – 105 infants exposed in 1st trimester – 12 (11.4%) major birth defects (4 expected). Possible association with hypospadias, but other factors (mother's disease, concurrent drug use and chance) may be involved.

The use of atenolol has been described frequently in pregnancy, no fetal malformations have been reported in these, however treatment did not occur in the 1st trimester.

Atenolol induced decreased fetal heart rate, increased pulsatory indices (and peripheral vascular resistance) of the fetal thoracic descending aorta, abdominal aorta and umbilical artery and a decrease in umbilical venous blood flow has been reported in several sources.

Low birth and placental weights, low birth length and IUGR have been reported with the use of atenolol in pregnancy. Some case reports were also associated with other factors such as pre-eclampsia.

Several reports of intrauterine death are given but little other details are available.

A randomised double blind study looking at atenolol versus placebo started at 34 weeks gestation showed no statistical difference in mean gestational age at delivery, hypoglycaemia, respiratory distress syndrome, hyperbilirubinaemia, birthweight or placental weight. Atenolol exposed infants did have significantly more bradycardia (39% versus 10%), no infants required treatment.

1 report of retroperitoneal fibromatosis in a foetus exposed to atenolol 100 mg daily from the second month of pregnancy. Drug was attributed to this due to the location of the mass being similar to that of fibroids reported in adults exposed to atenolol.

Propranolol (Human data suggest risk in 2nd and 3rd trimesters) (Cm*)

Propranolol readily crosses the placenta

A number of fetal and neonatal adverse effects have been reported with propranolol use in pregnancy, but other factors (mother's disease, concurrent drug use or a combination of these) may be involved. Doses of 160 mg daily (or more) seem to produce more serious complications but lower levels have been associated with toxicity.

Adverse effects seen in a meta-analysis of 23 reports included ($n = 167$):

IUGR (14%)

Hypoglycaemia (10%)

Bradycardia (7%)

Respiratory depression at birth (4%)

Hyperbilirubinaemia (4%)

Small placenta (2%)

Polycythaemia (1%)

Thrombocytopenia (0.6%)

Hyperirritability (0.6%)

Hypocalcaemia (with convulsions) (0.6%)

Blood coagulation defect (0.6%)

Michigan Medicaid surveillance study – 274 infants exposed in 1st trimester – 11 (4%) major birth defects (12 expected).

Respiratory depression was noted in 4 of 5 infants born to mothers who were given 1 mg IV propranolol just before C-section.

Fetal bradycardia has been reported in women having 1 mg/minute propranolol for 4 minutes for dysfunctional labour.

An increase in perinatal mortality has been described in a small study when compared with a control; however mothers were also using multiple other antihypertensives and had more severe renal disease and higher blood pressures in the propranolol group.

There are conflicting studies that either do or do not show a link with premature labour with propranolol use.

Acebutolol (Limited human data) (Bm*)

No human malformations attributed to acebutolol have been observed, but experience in the first trimester is lacking.

There have been reports of reduced birthweight with acebutolol.

In a comparison of 20 pregnant women treated with either acebutolol or methyldopa for mild to moderate hypertension, no differences were found in: pregnancy duration, birthweight, Apgar scores or placental weight. No evidence of neonatal bradycardia, hypoglycaemia or respiratory problems were seen, however, blood pressures, heart rates and blood glucose were significantly lower in the acebutolol group.

Bisoprolol (Human data suggest risk in 2nd and 3rd trimesters) (Cm*)

A case describing a 24 year old woman who took bisoprolol 5 mg/day (and naproxen and sumatriptan) in the first 5 weeks of pregnancy. The infant was delivered at 37 weeks by C-section and had a wide bilateral cleft palate, marked hypertelorism, a broad nose and bilateral but asymmetric toe abnormalities.

Carvedilol (Human data suggest risk in 2nd and 3rd trimesters) (Cm*)

No reports of use in human pregnancy have been located

Carvedilol is thought to cross the placenta

Celiprolol (Human data suggest risk in 2nd and 3rd trimesters) (B*)

In a small study celiprolol was shown to cross the placenta and reach 25–50% of maternal serum concentration in the foetus.

Esmolol (Compatible – maternal benefit > > embryo/fetal risk) (Cm)

Hypotension with esmolol is common (up to 50% in some trials) the potential for decreased uterine blood flow and resulting fetal hypoxia should be considered.

A case report of reduced fetal heart rate (139–144bpm to 131–137bpm) in a 22 week gestation foetus has been described during an esmolol infusion – bolus up to 2 mg/kg then 200 mcg/kg/min - No long lasting effects were see on this infant after birth.

Another case in a woman at 38 weeks gestation received 0.5 mg/kg bolus followed by a continuous infusion of 50 mcg/kg/min. Fetal heart rate before drug was 150–160bpm and increased to 170–175bpm 20 minutes after, at 24 minutes fetal heart rate fell to 70–80bpm and persisted despite stopping the infusion. After emergency caesarean section the infant's heart rate was 60bpm but recovered to 140bpm 60 seconds of age. Umbilical vein pH was 7.09.

Symptoms of β-blockade have been seen in an infant after delivery during maternal esmolol use; including: hypotonicity, weak cry, dusky appearance and apnoea with feeding (which resolved after 48 hours).

Symptoms of β-blockade have also been described in a foetus and neonate in which a mother was treated with 25 mcg/kg/minute esmolol during labour. Fetal bradycardia (100bpm) with loss of beat-to-beat variability was described. Apgar scores of 8 and 9 at 1 and 5 minutes respectively but neonate was hypotensive, mildly hypotonic, hypoglycaemic and fed poorly. All resolved at 36 hours of age. Fentanyl was also given during labour.

Metoprolol (human data suggest risk in 2nd and 3rd trimester) (Cm*)

Metoprolol readily crosses the placenta producing approximately equal maternal and fetal blood levels.

No fetal malformations attributable to metoprolol have been reported, but experience in the 1st trimester is limited.

Several reports are described were no fetal or neonatal complications were found.

Michigan Medicaid surveillance study – 52 infants exposed in 1st trimester – 3 (5.8%) major birth defects (2 expected).

A study compared 101 hypertensive pregnant women taking metoprolol ($n = 57$) or combined with hydralazine ($n = 44$) to 97 women taking hydralazine alone. Mean gestation was 34.1 weeks (13–41 weeks) for the metoprolol group and 32.5 weeks (12–40 weeks). The metoprolol group experienced a lower rate of perinatal mortality (2% versus 8%) and a lower incidence of IUGR (11.7% versus 16.3%). No signs or symptoms of βblockade were seen in the foetuses or neonates.

There are several conflicting studies that either do or do not show IUGR and low birthweight.

Nadolol (Human data suggest risk in 2nd and 3rd trimester) (Cm*)

Michigan Medicaid surveillance study – 71 infants exposed in 1st trimester – 1 (1.4%) major birth defects (3 expected).

One published report describes nadolol use in a single mother throughout pregnancy (20 mg/day) for hypertension (plus a diuretic). An infant was delivered at 35 weeks by C-section that was growth retarded, exhibited tachypnea (68 breaths per minute) and mild hypoglycaemia. Depressed respiration, bradycardia and hypothermia occurred at 4.5 hours of age and persisted for 72 hours. The cause of this could have been attributed to βblockade; however maternal condition and other drugs could not be excluded as causes.

Nebivolol

No information

Oxprenolol (Human data suggest risk in 2nd and 3rd trimester) (Cm*)

Oxprenolol crosses the placenta but only reaches 25–37% the serum concentration in the neonate compared with the mother.

No fetal malformations or other fetal adverse effects attributable to oxprenolol have been reported, but experience in the 1st trimester is limited.

When compared with methyldopa in pregnancy neonates are significantly larger (3051 g versus 2654 g), however the differences between these groups disappears after 10 weeks of treatment. Other studies have shown no difference in birth and placental weights, head circumference and Apgar scores.

Pindolol (Human data suggest risk in 2nd and 3rd trimester) (Bm*)

There are conflicting studies describing reduction in uterine artery vascular resistance.

No fetal malformations have been reported, but experience in the 1st trimester is lacking.

A study comparing pindolol to atenolol and acebutolol showed higher mean birthweights in the pindolol group. It is not known if this is linked to the drug potency, maternal condition or a combination of these or other factors.

Studies comparing pindolol to atenolol (started at 33 weeks) and hydralazine (started at 25 weeks) showed no difference in gestational length, birthweight, Apgar scores, caesarean section rates or umbilical cord blood glucose levels.

Alpha-blockers

Doxazosin (No human data) (Cm)

No reports of doxazocin in human pregnancy were located.

Indoramin

No information

Prazosin (Limited human data) (Cm)

Transfer of prazocin to the foetus is likely.

In three studies where prazocin was added to oxprenolol, atenolol or minoxidil and metoprolol for severe essential hypertension, gestational hypertension or maternal hypertension secondary to chronic nephritis no adverse effects attributable to the drugs were noted.

Another case of prazosin use with a beta-blocker for pheochromocytoma was described in the 3rd trimester. A healthy male infant was delivered by C-section.

Terazosin (No human data) (Cm)

No reports of terazosin in human pregnancy were located.

Calcium-channel blockers

Nifedipine (Human data suggest low risk) (Cm)

Michigan Medicaid surveillance study – 37 infants exposed in 1st trimester – 2 (5.4%) major birth defects (2 expected).

Use in the 2nd and 3rd trimesters has shown no affect on fetal or neonatal heart rates.

One study showed possible increases in perinatal death (130/1000), a lowered gestational age at birth, increase in C-section rates and growth retardation. However no link could be made between the above and the drug due to the severity of maternal disease and concomitant drug therapy.

Nifedipine has been shown to have a tocolytic action and has been reported (1 case) of potentiating the neuromuscular blocking action of magnesium.

Amlodipine (No human data) (Cm)

Amlodipine is likely to cross the placenta.

No reports of amlodipine in human pregnancy were located.

Diltiazem (Limited human data) (Cm)

A case of diltiazem (60 mg QDS) use in the 1st month of pregnancy (with Isosorbide dinitrate 20 mg QDS) for symptomatic myocardial ischemia which were continued throughout pregnancy resulted in no adverse fetal effects.

Michigan Medicaid surveillance study – 27 infants exposed in 1st trimester – 4 (14.8%) major birth defects (1 expected). Although small numbers there may be an association with cardiovascular defects but maternal disease, concurrent drug use and chance cannot be excluded as causes.

A multi centre cohort study of 81 infants who were exposed to calcium-channel blockers (13% diltiazem) was reported. Compared with controls no increase in the risk of major malformations was found.

When 22 women were treated with diltiazem versus 23 women with nifedipine as a tocolytic, no differences were found in the outcomes or maternal effects.

Felodipine (Limited human data) (Cm)

A multi centre cohort study of 81 infants who were exposed to calcium-channel blockers (1% felodipine) was reported. Compared with controls no increase in the risk of major malformations was found.

Another study with use started before or during the 1st trimester for chronic essential hypertension in 3 women showed growth restriction in all 3 infants; however maternal disease and concomitant use of other antihypertensives (beta-blockers) were assigned as the cause.

Isradipine (Limited human data) (Cm)

Isradipine crosses the placenta

27 women in the 3rd trimester with pregnancy-induced hypertension were treated with 2.5 mg BD for 4 days then 5 mg BD showed significant reduction in MAP without significant change in the uteroplacental or fetal blood flow. No adverse fetal effects were observed.

Another study in 14 women with either essential hypertension ($n = 3$) or pre-eclampsia ($n = 11$) at 5 mg OD for 4 days then 5 mg BD in the 3rd trimester showed no adverse effects in the newborn except one who's birthweight was below the 10th percentile and 2 who had transient hyperbilirubinaemia.

Several other studies are reported that show no fetal adverse effects.

Lacidipine

No information

Lercanidipine

No information

Verapamil (Compatible) (Cm)

Verapamil crosses the placenta.

There are several reports of verapamil use in the treatment of in utero supraventricular tachycardia (in conjunction with other agents) with no adverse fetal effects.

The use as antihypertensive and tocolytic in pregnancy has also been described without adverse fetal effects.

Michigan Medicaid surveillance study – 76 infants exposed in 1st trimester – 1 (1.3%) major birth defects (3 expected). This does not support an association between verapamil and congenital abnormalities.

A multi centre cohort study of 81 infants who were exposed to calcium-channel blockers (41% verapamil) was reported. Compared with controls no increase in the risk of major malformations was found.

The manufacturer also reports use in the 1st trimester without adverse fetal adverse effects, however hypotension has been reported with rapid IV boluses and may potentially cause reduced placental blood flow and fetal hypoxia.

Diuretics

Thiazide

Bendroflumethiazide (Limited human data) (Cm*) (D – for gestational hypertension)

See chlorothiazide

A study reported 1011 women who received 5 mg bendroflumethiazide a day from 30 weeks gestation until delivery (to prevent pre-eclampsia and eclampsia). No fetal adverse effects were noted.

Maternal hypovolaemia and diuretic use in pregnancy may be of concern.

Chlorothiazide (compatible) (Cm*)

Crosses the placenta – fetal levels are equal to that of the mother.

Published reports indicate that thiazides are infrequently used in the 1st trimester

Collaborative Perinatal Project (CPP) – 233 infants exposure in 1st trimester to thiazides (all mothers had cardiovascular disorders which may affect the results) – Increased risk of malformations for chlortalidone (20) and miscellaneous thiazides (35 – excluding chlorothiazide).

Michigan Medicaid surveillance study – 20, 48 and 567 infants exposed in 1st trimester to chlorothiazide, chlorthalidone and hydrochlorothiazide respectively:

Chlorothiazide - 2 (10%) major birth defects (1 expected)

Chlorthalidone - 2 (4.2%) major birth defects (2 expected)

Chlorothiazide - 24 (4.2%) major birth defects (22 expected)

Although the numbers are small it is not felt that these diuretics are linked to congenital malformations

When used in the 2nd and 3rd trimester adverse fetal effects are rare.

In 4035 women treated for oedema (drug not stated/hypertensive women excluded) significantly higher rates were found of: IOL, stimulation of labour, uterine inertia, meconium staining and perinatal mortality (not significant).

There are conflicting reports of neonatal thrombocytopenia

There are also concerns over possible: decrease in placental perfusion, neonatal hypoglycaemia, neonatal hypovolaemia and maternal/fetal serum electrolyte imbalances.

Chlortalidone

No information

Cyclopenthiazide

See chlorothiazide

Indapamide (Limited human data) (Bm*)

Michigan Medicaid surveillance study – 46 infants exposed in 1st trimester to indapamide – 3 (6.5%) major birth defects (2 expected).

Metolazone (Limited human data – Probably compatible) (Bm*)

See chlorothiazide

Xipamide

No information

Loop

Furosemide (Human data suggest low risk) (Cm*)

Crosses the placenta

Michigan Medicaid surveillance study – 350 infants exposed in 1st trimester – 18 (5.1%) major birth defects (15 expected). May support an association with furosemide and congenital defects (hypospadias), but other factors (mother's disease, concurrent drug use and chance) may be involved.

Furosemide has been used in the 2nd and 3rd trimesters for oedema, hypotension and toxaemia without fetal or newborn adverse effects.

Vasodilator drugs

Hydralazine (Human data suggest risk in 3rd trimester) (Cm)

Hydralazine crosses the placenta leading to concentrations equal or greater than that of the mother in the neonate.

No reports linking hydralazine with congenital defects were located.

Collaborative Perinatal Project (CPP) – 8 infant exposures in 1st trimester/136 infant exposures throughout pregnancy – no abnormalities found with 1st trimester use. 8 (5.8%) infants had defects when used in the 2nd and 3rd trimesters which is higher than expected, however the severity of the maternal condition may be responsible for this.

Michigan Medicaid surveillance study – 40 infants exposed in 1st trimester – 1 (2.5%) major birth defects (2 expected).

Neonatal thrombocytopenia and bleeding secondary to hydralazine ingestion throughout the 3rd trimester have been reported in 3 infants. This however may have been due to maternal hypertension.

Bosentan (No human data) (Xm)

Bosentan and its metabolites are expected to cross the placenta

No reports in human pregnancy were located.

Diazoxide (Human data suggest risk in 3rd trimester) (Cm)

Diazoxide readily crossed the placenta reaching fetal levels similar to that of the mother.

In one study the decrease in maternal blood pressure was sufficient to produce a state of clinical shock and endanger placental perfusion. Transient fetal bradycardia has been reported in other

studies following a rapid, marked decrease in maternal blood pressure. Fatal maternal hypotension has also been reported.

Rather than rapid IV boluses, small IV boluses at frequent intervals have successfully controlled maternal blood pressure without producing fetal toxicity.

Diazoxide is a potent relaxant of smooth muscle and may inhibit uterine contractions if given during labour (dose dependant effect); augmentation of labour with oxytocin may be required.

Neonatal hyperglycaemia has been reported after IV diazoxide use in the mother and can persist for 24–72 hours post delivery.

There are conflicting reports of alopecia, hypertrichosis and decreased ossification of the wrist in neonates exposed to diazoxide 19–69 days before delivery.

Appendix O

Safety of commonly used antihypertensive drugs during breastfeeding

Drug class/ name	M:P ratio	Relative infant dose	Reported paediatric concerns	Monitoring	Comments	Other
Thiazide diuretics						
Bendroflumethiazide,					Amount too small to be harmful[199] Large doses may suppress lactation[197;199;202] American academy of paediatrics classifies as compatible with breastfeeding[202]	
Chlortalidone	0.062	15.5%[198]	Nil[198]		Amount too small to be harmful[199] Long half life and may accumulate in milk[198] Highly plasma protein bound[198] Large doses may suppress lactation[197;199]	
Cyclopenthaizide					Amount too small to be harmful[199] Large doses may suppress lactation[199]	
Indapamide				Milk supply[197] Volume depletion[197]	No reports of exposure via breast milk[197] Manufacturer suggests avoid[199] May suppress lactation[202]	
Metolazone					Amount too small to be harmful[199] Large doses may suppress lactation[199]	
Loop diuretics						
Furosemide	0.5–0.82		Nil[197]		Amount too small to be harmful[199] Very unlikely that quantity transmitted in breast milk would produce effects in a nursing infant (relatively high doses used therapeutically in children) [197] Large doses may suppress lactation[197;199]	
Torasemide					No reports of exposure through breast milk[197] High plasma protein binding[197] May reduce milk supply[197]	
Other diuretics						

Drug class/ name	M:P ratio	Relative infant dose	Reported paediatric concerns	Monitoring	Comments	Other
Amiloride					No human exposure via breast milk reported[202] Passage into milk is expected[202]	
Beta-blockers						
Propranolol	0.2–1.54 0.33–1.65 (average 0.5)[197]	0.28%[197] 0.4%[198]	Nil[197]	Monitor for symptoms of beta-blockade[202]	Amount in breast milk low[197] American academy of paediatrics classifies as compatible with breastfeeding[202] Long-term effects on infant not known[202]	Circulatory problems and Hypoglycaemia reported in breastfeeding infants[198]
Acebutolol	1.9–9.2 (active metabolite 2.3–24.7)[197] 252 1.9–9.8 (1.5–24.7 active metabolite)[202]	3.6%[197]	Symptoms of beta-blockade have been observed (Hypotension, bradycardia, tachypnoea and drowsiness)[197;198;202]	Symptoms of beta-blockade[202]	Low protein binding and primary excretion via kidneys[198] Possible significant transfer to baby and accumulation in premature infants[198;199]	Possible toxicity due to beta-blockade but amount of most beta-blockers present in milk too small to affect infant[199]
Atenolol	1.5–6.8[197] 1.1–6.8[198]	6.6%[197]	One reported case of bradycardia, cyanosis and hypothermia required hospitalisation[197;198;202]	Symptoms of beta-blockade[202]	Low protein binding and primary excretion via kidneys[198] Some authors have failed to detect atenolol in breast milk[197] Possible significant transfer to baby and accumulation in premature infants[198;199;202]	
Bisoprolol			Nil[197]	Hypotension, bradycardia, other symptoms of beta-blockade[202]	No reports of use in lactating mothers[202]	
Carvedilol				Hypotension, bradycardia, other symptoms of beta-blockade[202]	No human data available[197;202] Highly lipid soluble and low molecular weight – transfer into milk expected[197]	
Labetalol	0.2–1.5[198] 0.8–2.6[197]	0.57%[197]	Nil[197;202]	hypotension and apnoea[197] Hypotension, bradycardia, other symptoms of beta-blockade[202]	Only small quantities excreted into breast milk[197;202]	
Metoprolol	3–3.72[197]	1.4%[197]	Nil[197;202]	Hypotension, weakness, bradycardia and other symptoms of beta-blockade[197;202]	Concentrated in breast milk – with milk levels approx [197] times that of maternal plasma[202] Maternal plasma levels are small and so infant dose remains low[197]	
Nadolol	4.6[197]	4.6%[197]		Symptoms of beta-blockade[202]	Long half life[197] Secreted into breast milk in moderately high amounts, possible significant transfer to baby and accumulation in premature infants[197;199] Milk levels 4.6 times greater than maternal plasma[202]	

Drug class/ name	M:P ratio	Relative infant dose	Reported paediatric concerns	Monitoring	Comments	Other
Oxprenolol	0.14–0.45[202]		Nil[202]	Bradycardia and other symptoms of beta-blockade[202]	Excreted into breast milk, amounts likely insignificant for the infant[202]	
Pindolol				Bradycardia and other symptoms of beta-blockade[202]	Manufacturer states present in breast milk[202] No reports of exposure though breast milk reported[202]	
Timolol	0.8–0.83[202]	1.1%[197]	Nil[197;202]	Hypotension, weakness, hypoglycaemia, sedation and depression Bradycardia and other symptoms of beta-blockade[202]	Levels in breast milk unlikely to be significant[197]	
Alpha-blockers						
Doxazocin					No reports of use in human lactation[202] Manufacturer suggests avoid[199]	
Prazocin					No reports of use in human lactation[202] Manufacturer reports small amounts in breast milk[202] Amount probably too small to be harmful[199] May reduce milk production[197]	
Terazosin					No reports of use in human lactation[202] Transfer into milk is expected[202]	
ACE inhibitors						
Captopril	0.032 0.012 [197;202]	0.02%[197]	Nil[197;202]	Hypotension[197]	Manufacturer suggests avoid[199] Excreted into breast milk in low concentrations[202] Can be used in breastfeeding[202] when first choice agents cannot be used or are ineffective (with monitoring)[197]	
Enalapril	0–0.14 (0.021–0.031 metabolite)[202] 0.013–0.025[197]	0.17%[197]	Nil[197]	Hypotension[197]	Amount probably too small to be harmful[199;202] Can be used in breastfeeding when first choice agents cannot be used or are ineffective (with monitoring)[197] Caution in preterm infants – risk of renal toxicity[197]	
Fosinopril			Nil[197]		Barely detectable levels present in breast milk (no values reported)[197] Manufacturer suggests avoid[199]	
Imidapril					Manufacturer suggests avoid[199]	
Lisinopril					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Moexipril					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	

Drug class/ name	M:P ratio	Relative infant dose	Reported paediatric concerns	Monitoring	Comments	Other
Perindopril					No reports of use during human lactation[202] Excretion into human breast milk should be expected (including its active metabolite)[202] Manufacturer suggests avoid[199]	
Quinapril	0.12 [197;202]	1.63	Nil[197]		Present in breast milk[202] Amounts available in breast milk clinically insignificant[202] Manufacturer suggests avoid[199]	
Ramipril	0.25%[197]		Nil[197]	Hypotension[197]	No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Trandolapril					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Angiotensin II receptor blockers						
Candesartan					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Eprosartan					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Irbesartan					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Losartan					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Olmesartan					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Telmesartan					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Valsartan					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202] Manufacturer suggests avoid[199]	
Calcium-channel blockers						

Drug class/ name	M:P ratio	Relative infant dose	Reported paediatric concerns	Monitoring	Comments	Other
Amlodipine			Nil[197]		No reports of use during human lactation[202] Excretion into human breast milk should be expected[197;202] Manufacturer suggests avoid[199]	
Diltiazem	0.2–0.92 13	0.8%[197]		Hypotension, bradycardia[197]	Significant amount present in milk – no evidence of harm but avoid unless no safer alternative[198] Present in breast milk at similar levels to that of maternal plasma[202]	
Felodipine					No reports of use during human lactation[202] Excretion into human breast milk should be expected[202]	
Isradipine			Nil[197]	Hypotension, fatigue, bradycardia and apnoea[197]	Manufacturer suggests avoid[199] No reports of use during human lactation[202] Excretion into human breast milk should be expected[202]	
Lercanidipine					Manufacturer suggests avoid[199]	
Nicardipine	0.08–0.75[197]	0.07%[197]			No reports of use during human lactation[202] Manufacturer suggests avoid[199;202]	
Nifedipine	13	1.83			Amount too small to be harmful (but manufacturer suggests avoid)[199;202]	
Verapamil	0.2–0.92 0.94[197]	0.15–0.98%[197]	Nil[197;202]	Hypotension, bradycardia, weakness[197]	Amount too small to be harmful[199]	
Other antihypertensives						
Clonidine	1.54 23	7.5%[197]	Nil[197;198;202]	Hypotension[197]	May reduce milk production[197] Manufacturer suggests avoid[199]	
Methyldopa	0.2–0.52 0.19–0.34[197]	0.11[197]	Nil[197;198]		Amount too small to be harmful[199]	
Moxonidine	1–2[198]				Manufacturer suggests avoid[199]	
Hydralazine	0.49–1.36[197] 0.52 1.44	1.2%[197]	Nil[197;198;202]	Hypotension, sedation, weakness[197]	Present in milk but not known to be harmful[199;202]	