

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

Final draft February 2010

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Acknowledgements

We thank the following colleagues at the NCC-WCH for their help and support in developing this guideline: Nicholas Cole, Paul Jacklin, David James, Sarah Latreille and Julia Saperia.

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 license 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*¹ 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 erythematosus 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 and angiotensin II receptor blockers (ARBs):

- that there is an increased risk of congenital abnormalities if these drugs are taken during pregnancy

¹In 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 ([date]). Informed consent should be obtained and documented.

- to discuss alternative antihypertensive treatment with their healthcare professional 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 reading device for measuring urinary protein levels by the dipstick test to diagnose pre-eclampsia in a secondary care setting.

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:

Management of pregnancy with gestational hypertension

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (\geq 160/110 mmHg)
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: <ul style="list-style-type: none"> • diastolic blood pressure less than 80–100 mmHg • systolic blood pressure less than 150 mmHg 	With oral labetalol† as first-line treatment to keep <ul style="list-style-type: none"> • diastolic blood pressure less than 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 dipsticks	At each visit using automated dipsticks	Daily using automated dipsticks
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: <ul style="list-style-type: none"> • kidney function, electrolytes, full blood count, transaminases, bilirubin

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:

Management of pregnancy with pre-eclampsia

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 (until blood pressure is less than 140/90 mmHg)	Yes (until blood pressure is less than 140/90 mmHg)	Yes (until blood pressure is less than 140/90 mmHg)
Treat	No	With oral labetalol† as first-line treatment to keep diastolic blood pressure less than 80–100 mmHg systolic blood pressure less	With oral labetalol† as first-line treatment to keep diastolic blood pressure less than 80–100 mmHg systolic blood pressure less

		than 150 mmHg	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 (clinical, biochemical and haematological) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia.

In women who have had pre-eclampsia offer 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 ranges from zero (0%) 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.

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.
- Significant proteinuria is if there is more than 300mg protein in a 24-hour urine collection.

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 the phrase 'offer birth' means 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

Antiplatelet agents

Advise women at high risk of pre-eclampsia to take 75 mg of aspirin*² 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 erythematosus 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*² 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.

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).]

Other pharmaceutical agents

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

* 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 ([date]). Informed consent should be obtained and documented.

- 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 and 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 their healthcare professional 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 diuretics:

- 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 their healthcare professional if they are planning pregnancy.

Tell women who take antihypertensive treatments other than ACE inhibitors, ARBs or chlorothiazide diuretics 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 antenatal steroids (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 use of antenatal antihypertensive treatment.
- review long-term antihypertensive treatment 2 weeks after the birth

If a woman has taken methyldopa^{†3} 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 dipstick for measuring proteinuria to diagnose pre-eclampsia in a secondary care setting.

Use 24-hour urine collection to quantify proteinuria if there is 1+ or more on automated urinary dipstick.

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.

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:

³ † 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 gestational hypertension

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: <ul style="list-style-type: none"> • diastolic blood pressure less than 80–100 mmHg • systolic blood pressure less than 150 mmHg 	With oral labetalol† as first-line treatment to keep <ul style="list-style-type: none"> • diastolic blood pressure less than 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 dipsticks	At each visit using automated dipsticks	Daily using automated dipsticks
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: <ul style="list-style-type: none"> • kidney function, electrolytes, full blood count, transaminases, bilirubin

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 antenatal steroids (if required) has been completed.

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 did not take antihypertensive treatment and have given birth, aim to keep blood pressure lower than 140/90 mmHg.

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.

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:

Management of pregnancy with pre-eclampsia

Degree of hypertension	Mild hypertension (140/90 to 149/99 mmHg)	Moderate hypertension (150/100 to 159/109 mmHg)	Severe hypertension (160/110mmHg or higher)
------------------------	----------------------------------------------	----------------------------------------------------	------------------------------------------------

Admit to hospital	Yes (until blood pressure is < 140/90 mmHg)	Yes (until blood pressure is < 140/90 mmHg)	Yes (until blood pressure is < 140/90 mmHg)
Treat	No	With oral labetalol† as first-line treatment to keep diastolic blood pressure less than 80–100 mmHg systolic blood pressure less than 150 mmHg	With oral labetalol† as first-line treatment to keep diastolic blood pressure less than 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

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 (clinical, biochemical and haematological) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia

Consultant obstetric staff should write a plan for 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 antenatal steroids 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 with severe pre-eclampsia after 34 weeks when their blood pressure has been controlled and a course of antenatal steroids has been completed (if appropriate).

Offer birth to women with mild or moderate pre-eclampsia 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 with mild or moderate pre-eclampsia 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 have given birth, aim to keep blood pressure lower than 140/90 mmHg. 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:

- 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.

In women with pre-eclampsia who have taken antihypertensive treatment and have given birth, continue antenatal antihypertensive treatment.

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.

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 with mild or moderate pre-eclampsia 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 urine dipstick 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 antenatal steroids 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 clinical features of severe pre-eclampsia:

- hypertension and proteinuria and
- symptoms of severe headache or
- problems with vision, such as blurring or flashing before the eyes or
- severe pain just below the ribs or vomiting or
- papilloedema or
- signs of clonus (≥ 3 beats) or
- liver tenderness or
- HELLP syndrome or
- platelet count falling to below 100×10^9 per litre or
- 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.

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.

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 criteria⁴:

Level 3	Severe pre-eclampsia and needing ventilation
Level 2	Step-down from level 3 or severe pre-eclampsia with any of the following complications: <ul style="list-style-type: none">- eclampsia- HELLP syndrome- haemorrhage- hyperkalaemia- severe oliguria- coagulation support- intravenous antihypertensive treatment- initial stabilisation of severe hypertension- evidence of cardiac failure- abnormal neurology

⁴ Adapted from Intensive Care Society, Standards and Guidelines 2002.

Level 1	- Mild or moderate pre-eclampsia - Ongoing conservative antenatal management of severe pre-term hypertension - Step-down treatment after the birth
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Chapter 11 Breastfeeding

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

Tell women who still require 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 require 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.

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 end-stage 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 ranges from zero (0%) 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.

Inter-pregnancy 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 (18.5–24.9kg/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

What is the best method to assess the presence and amount of proteinuria in women with new hypertension during pregnancy?

Why this is important

Most of the adverse outcomes of hypertension during pregnancy occur in women with pre-eclampsia. The test to determine the diagnosis is the key test in any assessment of new hypertension. Current use of dipsticks and 24-hour urine collection is challenged by modern near patient testing and by a lack of association between values traditionally regarded as abnormal and clinical outcomes.

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 versus 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 with mild or moderate pre-eclampsia give birth?

Why this is important

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

Women with mild or moderate pre-eclampsia 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 with mild or moderate pre-eclampsia 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

What is the best method to assess the presence and amount of proteinuria in women with new hypertension during pregnancy?

Why this is important

Most of the adverse outcomes of hypertension during pregnancy occur in women with pre-eclampsia. The test to determine the diagnosis is the key test in any assessment of new hypertension. Current use of dipsticks and 24-hour urine collection is challenged by modern near patient testing and by a lack of association between values traditionally regarded as abnormal and clinical outcomes.

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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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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 with mild or moderate pre-eclampsia give birth?

Why this is important

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

Women with mild or moderate pre-eclampsia 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 with mild or moderate pre-eclampsia 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 antihypertensive, 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 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 pathway

[The final published guideline will include some or all of the care pathway being developed for the quick reference guide.]

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 (December 2009) advise that anticipated benefit be weighed against the possible risks of its use in the first and second trimesters 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 (December 2009) 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 (December 2009) 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 (December 2009) 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 (December 2009) 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 (December 2009) 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 (December 2009) 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 mm Hg or greater on two occasions more than 4 hours apart or a single diastolic blood pressure above 110 mm Hg.¹ 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 that arises from 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.
- Significant proteinuria is if there is more than 300mg protein in a 24-hour urine collection.

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)². 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.

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).²³

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%.³ The rate for gestational hypertension is almost certainly under-reported, with rates between 4.2% and 7.9% recorded.³ 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.⁴⁻⁹ 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%.¹⁰ 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 United Kingdom (UK) appears to have fallen,¹¹ hypertension in pregnancy remains one of the leading causes of maternal death in the UK, Europe and elsewhere.^{12;13} 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,¹⁴ and a study conducted in the United States of America (USA) found that over half of admissions for acute renal failure, one quarter of admissions for coagulopathy and nearly one-third of admissions for ventilation or cerebrovascular disorders occurred in women with hypertensive disorders.¹⁵ 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.¹⁶

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.¹⁷

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 (4.9%) stillbirths in infants without congenital abnormality occurred in women with pre-eclampsia.¹⁸ While this may be an improvement from the late 1990s (7%)¹⁹ it still represents a significant burden. A similar trend in the stillbirth rate has been seen in Sweden.²⁰ Ten percent of women with severe pre-eclampsia give birth before 34 weeks.¹⁰ 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-eclampsia¹⁰ and 8-10% of all preterm births result from hypertensive disorders.²¹ Half of women with severe pre-eclampsia give birth preterm.²²

Small-for-gestational age (SGA) babies (mainly because of fetal growth restriction 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 birth weight for gestation.²²

There is national guidance on the care of women with severe pre-eclampsia or eclampsia²³ and on screening for hypertensive disorders during pregnancy.²⁴ 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 purposes 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)²⁴
- 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 general practitioners (GPs), nurses and 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/xxx) or from NICE publications on 0845 003 7783 (quote reference number xxx). [This paragraph to be completed in the final published guideline.]

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 62²⁴

- 'Intrapartum care', NICE clinical guideline 55²⁵
- 'Postnatal care', NICE clinical guideline 37²⁶
- 'Induction of labour', NICE clinical guideline 70²⁷
- 'Caesarean section', NICE clinical guideline 13²⁸
- 'Hypertension', NICE clinical guideline 34²⁹
- 'Diabetes in pregnancy', NICE clinical guideline 63³⁰
- 'Obesity', NICE clinical guideline 43²⁴⁰
- 'Smoking Cessation Services', NICE public health guidance 10³¹
- 'Maternal and Child Nutrition', NICE public health guidance 11³²
- 'Weight Management in Pregnancy' NICE public health guidance (in development; publication expected June 2010)³³
- 'Weight management following childbirth' NICE public health guidance (in development; publication expected July 2010)³⁴
- 'Quitting Smoking in Pregnancy and Following Childbirth' NICE public health guidance (in development; publication expected May 2010)³⁵

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.

Two external advisers were appointed by the GDG to advise on anaesthesia and obstetric critical care, respectively.

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 <http://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 <http://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.

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 2.1 Stages in the NICE guideline development process and versions of '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	✓	✓

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.

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 the corresponding publications 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 2.2 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 (for example, case reports, case series)
4	Expert opinion, formal consensus

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 different 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.³⁶ 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 to 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 to expectant management for women with mild to moderate pre-eclampsia at 34-37 weeks (see Appendix J)
- 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 (see Appendix K)
- cost effectiveness of automated urinalysis compared to visual urinalysis in the quantification of proteinuria in women with gestational hypertension (see Appendix L).

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 = $d/(c+d)$

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 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 (stroke, 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 intrauterine growth restriction (IUGR)
- Preterm birth at < 34 weeks
- Preterm birth (< 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.

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.

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 auto-immune 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.^{37;38}

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.³⁹ [EL=1+] In order to assess the effectiveness of different 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.³⁹ The meta-analysis of individual-patient data on risk reduction for pre-eclampsia with antiplatelet agents provided subgroup analysis by risk factor.⁴⁰ [EL=1+++] A further RCT focused on a specific population of women with the converting enzyme DD and a history of pre-eclampsia.⁴¹ [EL=1+] A Health Technology Assessment (HTA) report³⁷ 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) to reduce the risk of pre-eclampsia and its complications.³⁹ [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 to 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 out 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 sub-group 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, multiple pregnancy, a family history of pre-eclampsia and 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=4,121, 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 75mg a day or less), higher dose aspirin (defined as more than 75mg aspirin a day), and a third category (more than 75mg aspirin a 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 75mg 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, there was 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 to 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=5,061, RR=0.64, 95% CI 0.51 to 0.80). The combined effect across five studies (n=296) evaluating more than 75mg aspirin plus dipyridamole showed a statistically significant reduction in risk among women receiving this intervention compared to 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 to evaluate the optimal dosage. The subgroups considered were 60mg, 75mg, 100mg and 150mg. 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 75mg aspirin per day showed a statistically significant reduction in risk (8 studies, RR=0.65, 95% CI

0.51 to 0.83). The groups taking 100mg per day and 150mg per day showed no statistically significant reduction (100mg group, 13 studies, RR=0.71, 95% CI 0.50 to 1.02; 150mg 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 due to small numbers of studies.

The Cochrane systematic review³⁹ 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 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;⁴⁰ [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 women having their first pregnancy and with any high-risk factor (such as pre-existing kidney disease, diabetes, chronic hypertension or with a previous SGA infant), there was no statistically significant reduction in risk (RR=0.90, 95% CI 0.76 to 1.08). Women who had any high-risk factor in their second pregnancy showed a statistically significant risk reduction (RR=0.89, 95% CI 0.81 to 0.99). 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 post-partum 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;^{37:42} of these, one study⁴² was excluded because it was not a cost effectiveness study leaving one study that met the inclusion criteria, an HTA report by Meads et al (2008).³⁷ 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 to 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 to £278,515 for women not taking aspirin saving £7,852 per pregnancy. 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 1,000 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 and being a teenager). One study⁴⁰ 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 to 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 75mg/day (although the two higher dose groups may have been underpowered to detect a difference due to 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, auto-immune disease such as systemic lupus erythematosus (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, body mass index (BMI) 35 or more at first visit, and multiple pregnancy (see 'Antenatal care', NICE clinical guideline 62).^{24;43} 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 considered 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 in nulliparous women⁴⁴ and twin pregnancy in nulliparous women).⁴⁵ 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 60mg and 75mg and those using 100mg and 150mg 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 75mg per day is optimal. This is the lower dose available in the UK (the higher dose being 300mg per 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 which lead to the clinical syndrome of pre-eclampsia begin in the first half of the second trimester of pregnancy and there 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

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 erythematosus 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.

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).]

Research recommendations

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 effectiveness of nitric oxide donors and precursors for preventing pre-eclampsia.⁴⁶ [EL=1+] Studies were included in the review regardless of gestation at trial entry, as were women with normal and high blood pressure and women with 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 developed gestational hypertension. The risk of developing pre-eclampsia was unclear for another two studies and where the quality 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) in 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.⁴⁷ [EL=1+]

Pregnant women with normal or high blood pressure but without proteinuria were included. Women who received any progesterone were compared to 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 1,836 women, evaluated the effect of diuretics for preventing pre-eclampsia.⁴⁸ [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=1,391) investigated the effect of diuretics compared to 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=1,475) 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 and a history of pre-eclampsia, investigated the effect of low-molecular-weight heparin (LMWH) on the recurrence rate of pre-eclampsia.⁴¹ [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 fetal growth restriction (RR=0.22; 95% CI 0.08 to 0.61), and an even bigger reduction for fetal growth restriction 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 are unlikely to be now regarded as appropriate options for therapy.

The evidence for the use of LMWH, though 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 they do not recommend its use.

Recommendations

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.⁴⁹⁻⁵³ [EL=1+] A prospective cohort study was also identified in relation to the use of folic acid supplementation.⁵¹ [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 62²⁴ and 'Maternal and Child Nutrition', NICE public health guidance 11).³²

Calcium

A Cochrane systematic review of 12 RCTs, involving 15,206 women, evaluated the effectiveness of calcium in risk reduction for pre-eclampsia.⁴⁹ [EL=1+] Pregnant women at different levels of risk of developing pre-eclampsia were included in the analysis comparing 1.5g to 2g 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 which 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 biggest 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=8,302), however, 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 10 RCTs, involving 6,533 women, evaluated the risk reduction effects of antioxidants on pre-eclampsia.⁵⁰ [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 (<37 weeks). Nine studies (n=5,446) 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=4,272) investigated severe hypertension (RR=1.39, 95% CI 0.85 to 2.30) and five studies (n=5,198) investigated preterm birth (<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 vitamin 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 vitamin C and E alone (four studies, n=4,655), vitamin C alone (one study, n=200), red palm oil (one study, n=113) and selenium (one study, n=100). Similarly, no statistically significant effect was found for vitamin C and E alone for preventing severe pre-eclampsia (two studies, n=2,495).

An RCT from Brazil, including 734 women, investigated the effect of vitamin C and E on the incidence of pre-eclampsia.⁵⁴ [EL=1+] Women were randomised to receive both vitamin C (1,000 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 2,951 women evaluated the association between folic acid supplementation early in the second trimester and the risk of developing pre-eclampsia.⁵¹ [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 1.0mg 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 2,755 women, evaluated the effect of marine oil and other prostaglandin precursors on risk reduction for pre-eclampsia.⁵² [EL=1+] Orally administered marine oils (fish oils or algal oils) were compared with placebo or no marine oil. Across five studies (n=1,831) 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=1,683) 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.⁵³ [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 800mg per 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 show 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, though the significance of the effect is influenced by pre-eclampsia risk status or diet, for which trial size is a marker. 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, though 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 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 suggests 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 has been 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 though 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 (vitamin C and E). No benefit in terms of prevention of hypertensive disorders has been 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.

Recommendations

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 recommendations

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).

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.⁵⁵ [EL=1+] Women were eligible for randomisation if they had one or more of the following: two diastolic blood pressure recordings >85 mmHg; weight gain > 1kg/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 (e.g. twin pregnancy, diabetes, chronic hypertension or kidney disease) were excluded. The included women were nulliparous and had a diastolic blood pressure < 90mmHg at their first antenatal visit, which took place before 20 weeks. The study compared advice to reduce dietary salt intake to 50mmol per day with advice to continue a normal diet. Adherence was tested by checking urinary sodium excretion. Mean sodium concentration after randomisation was 84mmol/day (target 50mmol/day) in the low sodium group and 124mmol/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 to advise dietary salt reduction in chronic hypertension.

Recommendations

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.⁵⁶ [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 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 soya protein 25g, 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 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.⁵⁷ [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, 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 <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 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 18.5-24.9kg/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)²⁴⁰ during pregnancy. Weight management during and after pregnancy is also being considered in NICE public health guidance that is under development ('Weight Management in Pregnancy' NICE public health guidance (publication expected June 2010)³³ and 'Weight management following childbirth' NICE public health guidance (publication expected July 2010)).³⁴

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.⁵⁸ [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 out 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 to 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, though 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 end points. 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.

Recommendations

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)²⁴ and additional factors, which for hypertension includes 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 periconceptual period and during the first trimester of pregnancy.

The literature search identified 136 articles of which 10 were retrieved. A further 5 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.⁵⁹ [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. Thus, 29,096 infants with no exposure to antihypertensive drugs at any time during gestation were included in the study. Two hundred and nine infants 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 to infants who were not exposed to any antihypertensive treatment (RR=2.71; 95% CI 1.72 to 4.27).

Another study conducted in the USA⁶⁰ [EL=3] included all adverse outcomes associated with enalapril use in pregnancy that were submitted to the United States Food and Drug Administration (FDA) during 1986 and 2000 (108 reports). Adverse pregnancy outcomes were defined as any embryo-fetal adverse outcome, any congenital malformation, IUGR and preterm delivery before 37 weeks. Of the 108 cases, 88.9% had embryo-fetal adverse outcomes defined as embryo-fetal death, spontaneous abortion, 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 (<37 weeks).

A case series of 19 newborns of women exposed to ACE inhibitors was compiled in the USA.⁶¹ [EL=3] These originated from all women aged 15-44 years enrolled in Tennessee Medicaid who delivered a live-born or stillborn infant between 1983 and 1988 and who were exposed to ACE inhibitors during pregnancy. Out of the 19 infants, two were born preterm with serious life threatening conditions. One preterm infant had kidney problems requiring dialysis; the other had microcephaly and occipital encephalocele. One infant was born at term but was hypoglycaemic; 16 infants were born at term and appeared normal.

A further small case series conducted in the UK included 18 women (19 pregnancies) who were exposed to ACE inhibitors during pregnancy⁶²[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). No congenital malformations or any cases with kidney dysfunction were reported. There were no congenital malformations or neonatal problems in infants of women who were exposed to ACE inhibitors throughout pregnancy.

Angiotensin II receptor blockers

One systematic review was identified in which ARBs were used in pregnancy.⁶³[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 with a favourable outcome ($p=0.04$). Of the included cases, 37 women (57.8%) had favourable and 27 (42.2%) had unfavourable outcomes (mainly congenital malformations such as limb, skull, face, kidney and pulmonary defects). Of the women with unfavourable outcomes, 10 were exposed to valsartan, nine to losartan, six to candesartan and two to irbesartan. Of the women with favourable outcomes, six were 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).

Table 4.1 Safety data for antihypertensive drugs in pregnancy

Drug	Route	Safety data
<i>Centrally acting</i>		
Methyldopa	Oral	- Mild hypotension in babies 2 days life - No obvious association with congenital abnormalities
<i>Beta blockers</i>		
Labetalol	Oral / IV	-No obvious association with congenital abnormalities - Rare mild hypotension in first 24hrs of life - Very rare hypoglycaemia
Atenolol	Oral	-No obvious association with congenital abnormalities - Low birth weight/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
<i>Alpha blockers</i>		
Prazosin	Oral	- No obvious association with congenital abnormalities
<i>Calcium-channel blockers</i>		
Nifedipine	Oral	- No obvious association with congenital abnormalities
Amlodipine	Oral	- No reports
Verapamil	Oral/ IV	- No obvious association with congenital abnormalities
<i>Diuretics</i>		
Chlorothiazide	Oral	- Possible association with congenital abnormalities - Possible neonatal thrombocytopaenia - Possible neonatal hypoglycaemia/hypovolaemia - Possible maternal/fetal electrolyte imbalances
Bendrofluazide	Oral	- No adverse fetal effects - Maternal hypovolaemia
Furosemide	Oral / IV	- No obvious effects
<i>Vasodilators</i>		
Hydralazine	IV	- No obvious association with congenital abnormalities
Diazoxide	IV	- May inhibit uterine contractions - Profound maternal hypotension possible - Neonatal hyperglycaemia reported

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 to 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 gestation was on average 9 weeks longer in women not taking ARBs compared those who did. Overall, 42% of pregnancies exposed to ARBs had unfavourable outcomes (defined as any congenital malformation).

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 premature delivery.

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. Chlorothiazides may carry the risk of congenital abnormality, neonatal thrombocytopenia, hypoglycaemia and hypovolaemia.

Recommendations

Tell women who take angiotensin-converting enzyme (ACE) inhibitors and 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 their healthcare professional 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 diuretics:

- 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 their healthcare professional if they are planning pregnancy.

Tell women who take antihypertensive treatments other than ACE inhibitors, ARBs or chlorothiazide diuretics 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).²⁹

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)²⁹ in relation to dietary salt intake. The rationale for this being that chronic hypertension in pregnancy has the same pathogenesis as chronic hypertension in non-pregnant people.

Recommendations

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 out.⁴⁰ [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 (e.g. kidney disease, diabetes, immune disorder, chronic hypertension) or obstetric risk factors early in their current pregnancy (e.g. 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). Whilst 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 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 per 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++] which 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 which 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 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.⁶⁴ [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; 91% of the women had received various antihypertensive treatments before pregnancy, including diuretics, methyldopa, various beta-blocker and other antihypertensive drugs. Methyldopa was started at 750 mg/day and increased as needed to a maximum of 4 gm/day to achieve a target systolic blood pressure of < 140 mmHg and diastolic blood pressure of <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 >160 mmHg or diastolic pressure >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 abruptio placentae, preterm birth (<37 weeks), SGA and perinatal deaths.

A small RCT (n=25) conducted in the USA investigated the efficacy of methyldopa in chronic hypertension.⁶⁵ [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 < 100 mg), presumed chronic hypertension, gestational age below 34 weeks and singleton pregnancy. Thirteen women received one tablet 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 (2g) to maintain blood pressure ≤140/90 mmHg. Pre-eclampsia was defined as a sudden rise in systolic blood pressure by 30 mmHg or in diastolic pressure by 15 mmHg, and increased weight gain (>2lbs per 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 statistical significant difference was found for birthweight and ponderal index (both corrected for gestational age).

Labetalol

An RCT investigated the effectiveness of labetalol and methyldopa in chronic hypertension.⁶⁴[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 abruptio placenta, preterm birth (<37 weeks), SGA and perinatal deaths.

Atenolol

A UK RCT evaluated the effectiveness of atenolol in women with chronic hypertension.⁶⁶ [EL=1-] Women were recruited for 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 atenolol daily, increasing until blood pressure was below 140/90 mmHg or a dose of 200 mg daily 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 901g; 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 (i.e. after treatment; $p=0.08$). Babies born to mothers who received atenolol were on average 901g lighter (mean birth weight 2629g) than babies born to women receiving placebo (mean birth weight 3530g).

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.⁶⁷ [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 included women 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 gm 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 and stopping treatment 1/10; $p >0.05$), nor for any of the other outcomes investigated (birthweight, SGA, 5-min 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.⁶⁸ [EL=1-] Inclusion criteria were: a documented history of hypertension (blood pressure $\geq 140/90$ mmHg) before pregnancy, the finding of hypertension in at least two consecutive measurements more than 24 hours apart before 20 weeks, 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, 10 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 untreated group in the analysis. The intervention was continued antihypertensive treatment. Four women in the treatment group (4/29) had pregnancy-aggravated hypertension (defined as increase in diastolic blood pressure to a level above 100 mmHg in two consecutive measurements 6 hours or more apart) compared to (13/29) women in the no-treatment group ($p < 0.05$). None of the other outcomes investigated (premature labour < 37 weeks, birthweight below 2501g, fetal distress, 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 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 RCT⁶⁹ [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 <130/80 mmHg) or less tight blood pressure target ($n=62$; target blood pressure 130-139/80-89 mmHg). There were no 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 versus 35.8 ± 2.2 , $p < 0.05$) and were less likely to be born preterm (RR 0.52; 95% CI 0.28 to 0.99). There were no significant differences between groups in terms of intrauterine fetal death, admission to NICU, or fetal growth restriction.

One multicentre RCT⁷⁰ [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 (dBP 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), 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; goal dBp 100 mmHg) or 'tight' (n= 66; target dBp 85 mmHg) control of blood pressure. There were no significant differences in baseline characteristics between the two groups. No significant differences were found between the two groups in terms of gestational age at delivery (36.9 weeks \pm 3.0 versus 36.3 weeks \pm 3.3, p= 0.278), serious perinatal complications (13.6% versus 21.5%; RR=0.63, 95% CI 0.29 to 1.36), care in neonatal intensive care units (22.7% versus 34.4%; 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 (15.2% versus 18.5%; 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 (30.3% versus 29.2%, RR =1.04, 95% CI 0.61 to 1.76) or in infants with birthweight less than 2500 g (34.9% versus 49.2%, RR=0.71, 95% CI 0.47 to 1.07). Pre-eclampsia was reported in 62.1% of the 'less tight' group and 52.3% of the 'tight' group (RR=1.34, 95% CI 0.94 to 1.89), and severe hypertension in 57.6% 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 3,773 women taking antihypertensives (including methyldopa, acebutolol, atenolol, labetalol, metoprolol, oxprenolol, pindolol, propranolol, bendrofluazide, chlorothiazide, hydrochlorthiazide, ketanserin, hydralazine, isradipine, nicardipine, nifedipine, verapamil and clonidine).⁷¹ [EL=1+] The aim of the study was to estimate the association of treatment-induced 'MAP' (assumed to denote mean arterial pressure, although this was not stated explicitly) 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 due to outlying results, a 10mmHg fall in MAP 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 MAP 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 at 'tight' versus 'less tight' control of hypertension in 120 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 fetal growth restriction.

Another RCT [EL 1+] looked at 'tight' versus 'less tight' control of hypertension in 132 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 neonatal intensive care units, 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 mm Hg fall in mean arterial pressure in women taking antihypertensives (including methyldopa, acebutolol, atenolol, labetalol, metoprolol, oxprenolol, pindolol, propranolol, bendrofluazide, chlorothiazide, hydrochlorthiazide, ketanserin, hydralazine, isradipine, nicardipine, nifedipine, verapamil and clonidine) was associated with a 145g 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 to continued normal activities at home.⁷² [EL=1+] Two hundred and eighteen women with singleton pregnancies and blood pressure \geq 140/90 mmHg, without proteinuria and between 28 and 38 weeks gestation were included in the study; of these 33 had chronic hypertension. Women who were symptomatic, had a diastolic blood pressure \geq 100 mmHg, 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 was that further research was 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 different antihypertensive agents.

Level of blood pressure control

The GDG considered that the effect on fetal growth with some agents (mainly beta-blockers) was 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, bendrofluzide, chlorothiazide, hydrochlorothiazide, ketanserin, hydralazine, isradipin, nifedipine, verapamil and clonidine), the more 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 34,²⁹ 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 $\geq 20\%$ 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 recommendations

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 fetal growth restriction, fetal hypoxia and ultimately fetal death.

Uterine artery Doppler velocimetry

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

One diagnostic study⁷³ [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 > 160/110 mmHg). Women with autoimmune disorders treated with corticosteroids, fetal chromosomal abnormalities and rhesus isoimmunisation were excluded. All women underwent uterine Doppler velocimetry at 23-24 weeks.

Using resistance index to interpret Doppler velocimetry results (abnormal > 90th percentile of 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 study⁷⁴ [EL II] examined a group of 78 pregnant women with chronic hypertension (dBP>90 mmHg). Uterine Doppler velocimetry was conducted at 24-25 weeks and endpoint outcomes were pregnancy-aggravated hypertension (dBP increase > 15 mmHg), superimposed pre-eclampsia, IUGR or abruptio placentae. When used for any complication, the resistance index (abnormal > 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 studies⁷⁵⁻⁷⁷ [EL II] investigated the use of uterine Doppler velocimetry at 22-24 weeks gestation in women with high-risk pregnancy (previous pre-eclampsia, previous stillbirth, previous abruptio placentae, previous IUGR, chronic hypertension, diabetes, autoimmune disease, kidney disease, habitual abortion).

Using resistance index gave a sensitivity of 78-97% and specificity of 42-71% for prediction of pre-eclampsia. One study⁷⁷ (n=116) reported data on the use of resistance index in predicting IUGR, with a sensitivity of 84% and specificity of 39% for small for gestational age babies.

The evidence is summarised in Tables 4.2 and 4.3.

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

Study	Population Demographic characteristics	GA	Index		Pre-eclampsia	IUGR	Notes
Caruso 1996 Country: Italy	N=42 chronic hypertension: 37 mild (BP 140-159/90-109 mmHg), 5 severe (BP>160/110 mmHg). Age 32(23-44)	23-24 wks	RI: abnormal > 90th percentile Reference group: 1,084 healthy pregnant women	For high risk women: Sens: Spec: PPV: NPV	78% 45% 28% 88%	50% 39% 8% 88%	Exclusion: autoimmune disease, fetal chromosomal abnormalities, Rh isoimmunisation Antihypertensive therapy was discontinued and restarted if BP>160/110 mmHg. Endpoints: SPE
Parretti 2003 Country: Italy	N=144, previous PET (n=87), previous stillbirth (n=22), previous abruptio placentae (n=11), previous fetal growth restriction (n=24) Age: 34.5 (27-41), gravidity 2(2-3), parity: 1(1-2)	24 wks	RI: abnormal \geq 0.58	Sens: Spec: PPV: NPV:	77.8% 67.6% 44.4% 90.1%	Not reported	Exclusion: smoking, kidney disease, CVD, DM, multiple pregnancy, fetal chromosomal abnormalities, or if already on low-dose aspirin PE= BP> 140/90mmHg, proteinuria >0.3 g/24h. Endpoint: PE
Caforio 1999 Country: Italy	N= 335, CH (n=89), PE (n=76), IDDM (n=58), autoimmune disease (n=53), SLE (n=17), renal disease (n=34), previous stillbirths (n=91), IUGR (n=20) and habitual abortion (n=119) Age 31 \pm 4.8 yrs	N=249 at 22-24 wks	RI: abnormal > 90th percentile	Sens: Spec: PPV: NPV:	97% 71% 31% 99%.	77% 72% 37% 94%(Endpoint: birthweight <1,750 gm)	Exclusion: congenital defects, chromosomal abnormalities, multiple gestations, infections, Rh isoimmunisation, nonimmune hydrops, premature rupture of the membranes, intrauterine deaths or delivery prior to 26 weeks gestation. (reference ranges previously obtained in our laboratory from 1,084 healthy pregnancy) Endpoint: PE
Coleman 2001 Country: New Zealand ⁷⁷	N=116, CH (n=69), previous recurrent PE (n=24), previously early-onset PE requiring delivery at \leq 32 weeks (n=25), previous placental abruption (n=10), kidneydisease (n=40), SLE (n=13), antiphospholipid syndrome (n=5) Age: 31 (19-43) yrs. 31/116 were nulliparous and 18% smoked	22-24 wks	RI: any abnormal >0.58 Bilateral notch	Sens: Spec: PPV: NPV: Sens: Spec: PPV: NPV	91% 42% 37% 92% 29% 86% 47% 74%	84% 39% 33% 87% 36% 89% 53% 79%	Exclusion: multiple pregnancies and pregnancies with recognised fetal abnormalities. Endpoint: PE * Data for Both RI >0.58, any notch, and Any RI and any notch are also reported.

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	during pregnancy.						
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Table 4.3 Use of uterine Doppler velocimetry to predict pregnancy-aggravated hypertension, superimposed pre-eclampsia, IUGR and abruptio placentae in women with chronic hypertension

Study	Population Demographic characteristics	Gestational age	Index		Pre-eclampsia	IUGR	Notes
Frusca 1998 Country: Italy ⁷⁴	N=78 chronic hypertension (dBP>90, no proteinuria)	24-25 wks	RI: abnormal=>2SD above normal mean for GA	Sens: Spec: PPV: NPV:	76% 84% 64% 91%		Exclusion: multiple pregnancy, fetal structural or chromosomal abnormalities Pre-pregnancy antihypertensives were stopped at first visit (7-10 wks), restarted if dBP>100 mmHg. All women took 50mg/day aspirin from 12th wks Endpoints: pregnancy aggravated hypertension (dBP increase >15 mmHg), superimposed PE (SPE), IUGR and abruptio placentae.

Evidence statement

One diagnostic study [EL II] showed that uterine 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

A few 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 including 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.

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 62²⁴ 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 the woman with pre-eclampsia (see Chapter 7).

Recommendations

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 fetal growth restriction 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 antenatal steroids (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 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 <http://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,⁷⁸ 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 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^{†5} to treat chronic hypertension during pregnancy, stop within 2 days of birth and restart the antihypertensive treatment the woman was taking before planning 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.

⁵ †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 300mg protein in a 24-hour period, and this is included in definitions of pre-eclampsia.

This section reviews the evidence on testing for proteinuria.

5.2 Measurement of proteinuria

5.2.1 Visual and automated dipstick tests

Clinical effectiveness

Visual dipstick test

One systematic review⁷⁹ [EL=Ia] investigated the value of point-of-care dipstick urinalysis in the prediction of significant proteinuria. Seven diagnostic test studies were included (n=1,841 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 pregnancies complicated by kidney disease. Six studies looked at visual dipsticks and two looked at automated dipsticks. The reference standard cut-off point for significant proteinuria was taken as 300 mg/24hrs or 300 mg/l in 24-hour urine collection. When 300mg/l was not used as the definition for significant proteinuria these studies were not included in the systematic review.

At a reference standard cut-off of 300 mg/24 hrs, with proteinuria of 1+ on a visual dipstick (six studies, n= 1,738), sensitivities of 55% (37-72%, n= 680) specificities of 84% (57-95%, n= 1,058) were reported. A PPV of 72% (53-86%), a NPV of 30% (23-40%) and significant LR_s were also found (LR₊ 3.48, 1.66 to 7.27; LR₋ 0.6, 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 new-onset hypertension.⁸⁰ [EL=Ib] All women had a systolic blood pressure greater than 140 mmHg or a diastolic blood pressure greater than 90 mmHg. The 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. Sensitivity, specificity, positive and negative LR 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.⁸¹ [EL=Ib] The study included women with gestational hypertension as well as those with pre-eclampsia. Routine urine dipstick analysis was performed by a midwife before a 24-hour urine sample was collected over the next day. It was not reported if the first morning void of urine was used in the analysis. The sensitivity, specificity, positive LR and negative LR 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 dipstick test

The same systematic review⁷⁹ [EL=Ia] that looked at the visual dipstick test (see above) investigated the use of an automated dipstick and investigated the value of point-of-care dipstick urinalysis in the prediction of significant proteinuria.

At a reference standard cut-off of 300 mg/24 hrs, with proteinuria of 1+ on an automated dipstick (one study, n= 171), a sensitivity of 82% (n= 77) and specificity of 81% (n= 94) was reported. A PPV of 77.7%, NPV of 15.6% and significant likelihood ratios were also reported (LR+ 4.27, 95% CI 2.78 to 6.56; LR- 0.22, 95% CI 0.14 to 0.36).

A prospective diagnostic study⁸⁰ conducted in the UK [EL=Ib] looked at visual and automated microalbumin dipstick tests. The visual dipstick had a sensitivity of 51% (95% CI 39% to 62%) whereas the automated reading (Multistix 8SG) had a sensitivity of 82% (95% CI 71% to 90%). The specificity for the visual dipstick was 78% (95% CI 68% to 86%) and 81% (95% CI 71% to 88%) for the automated reading. The diagnostic accuracy (measured by the area under the receiver-operator characteristic (ROC) curve) was 0.67 (95% CI 0.59 to 0.75) for the visual dipstick and 0.84 (95% CI 0.79 to 0.90) for the automated dipstick. Comparing the visual dipstick (using a threshold of 3.4 for albumin:creatinine ratio) with the automated dipstick showed a sensitivity of 49% (95% CI 38% to 61%), specificity 83% (95% CI 74% to 90%) and diagnostic accuracy 0.67 (95% CI 0.60 to 0.74) for the visual dipstick and 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) for the automated dipstick.

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 dipstick 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;⁷⁹ 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 associated mortality and morbidity and costs associated with undiagnosed pre-eclampsia.

We conducted separate analyses for 1+ versus 2+ thresholds for visual and automated dipsticks. The analysis showed that a threshold of 1+ was cost-effective when compared to 2+ for both visual and automated urinalysis. The estimated incremental cost effectiveness ratios (ICERs) were £10,767 and £8,650 for visual and automated urinalysis, respectively.

Having established the cost effective threshold, we compared automated urinalysis with visual urinalysis using a 1+ threshold. The base-case analysis showed that overall, automated was the less expensive strategy compared to 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 to visual urinalysis.

Evidence statement

One systematic review⁷⁹ [EL=Ia] investigated the value of point-of-care dipstick urinalysis in the prediction of significant proteinuria, as shown in Table 5.1.

Table 5.1 Summary of Waugh et al's (2004) systematic review⁷⁹

Reference Cut Off	Type of Dipstick	Proteinuria Level	Predictive Results	
300 mg/24hrs	Visual 6 studies n= 1,738	≥1+	Sensitivity	55%
	Automated 1 study n= 171	≥1+	Specificity	84%
PPV			72%	
			NPV	30%
			LR+	3.48 (95% CI 1.66 to 7.27)
			LR-	0.6 (95% CI 0.45 to 0.8)
			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)

A prospective diagnostic study [EL=Ib] showed that 1+ proteinuria on a visual dipstick had a sensitivity, specificity, positive LR and negative LR 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 and automated dipsticks using a threshold of 3.4 for the albumin:creatinine ratio. The visual dipstick showed a sensitivity of 49% (95% CI 38% to 61%), specificity 83% (95% CI 74% to 90%) and diagnostic accuracy 0.67 (95% CI 0.60 to 0.74). The automated dipstick, however, showed a sensitivity of 58% (95% CI 47% to 70%), a specificity of 83% (95% CI 74% to 90%) and an accuracy of 0.72 (95% CI 0.65 to 0.79).

The GDG's health economic analysis showed that the 1+ threshold is cost effective when compared with 2+ for visual (£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.

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.⁸²⁻⁸⁴ One study [EL=II] was conducted in Thailand⁸³, one [EL=III] was conducted in the USA⁸⁴ and one [EL II] was conducted in Nigeria.

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.⁸³ [EL=II] Women included in this study had either a resting blood pressure of $\geq 140/90$ mmHg 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 value for 4-hour protein:creatinine ratio to predict significant proteinuria (defined as ≥ 300 mg protein in 24-hour urine collection) determined by a ROC curve was 0.30. Sensitivity was 81% and specificity 88% (no CIs were reported). At this cut-off, the positive and negative LR_s 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 to total protein measured in a 24-hour collection.⁸⁴ [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; 25 women had pre-eclampsia, of whom two (7%) had mild pre-eclampsia, 16 (55%) had severe pre-eclampsia, and seven (24%) had superimposed pre-eclampsia. Of the remaining four participants, two (7%) had isolated chronic hypertension, and two (7%) 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 of the time of the day. Significant protein in the 12-hour sample was taken as total protein >150 mg. Sensitivity was 96% and specificity 100%. CIs were not calculated because one cell contained the value zero.

One prospective diagnostic study⁸² [EL II] conducted in Nigeria compared urine protein from 2-hour and 12-hour samples compared with 24-hour samples for diagnosing pre-eclampsia. The study included 86 women (gestational age ≥ 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, urinary tract infection, women that had vulva or vaginal cleansing with antiseptics or skin cleansers were excluded (n=12). Urine was collected from women at 9 am on the day after admission, then 2 hours later, 12 hours later and 24 hours later. The first three samples were compared to the 24-hour protein sample in detecting significant proteinuria. In comparison with the gold standard test (24-hour urine collection), the 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 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 compared to a 24-hour urine collection. The 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 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 UK study [EL=Ib] evaluated the diagnostic value of the visual microalbumin dipstick,⁸⁰ and an Italian study [EL=III] examined the diagnostic value of 24-hour urine microalbumin excretion measured in a 24-hour sample.⁸⁵

A well conducted UK prospective study included 171 women at 20 weeks or more and new-onset hypertension.⁸⁰ [EL=Ib] All women had a sustained systolic blood pressure of greater than 140 mmHg or a diastolic blood pressure greater than 90 mmHg. Women with chronic hypertension were excluded. A visual 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 300mg per 24 hours. The threshold value chosen for the albumin:creatinine ratio was 3.4 and the sensitivity, specificity, positive and negative LR 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.

Another Italian study investigated the diagnostic accuracy of the albumin excretion rate, including 108 pregnant hypertensive women, of whom 40 (37%) had chronic hypertension.⁸⁵ [EL=III] The included women were at 28-30 weeks and had proteinuria below 0.3g/24h 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 to 24-hour urine protein excretion. The threshold for the albumin excretion rate of 49mg/l 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 the 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 review⁸⁶ [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 (QADAS) tool. Case-control studies were excluded, as was one study that was not in English or French.

Spot protein:creatinine ratio

Thirteen studies (n= 1,214) looked at spot protein:creatinine ratio. No consistency was found with how cut-off points were reported. Eight different cut-off points were used (median 24 mg/mmol; 17-57 mg/mmol). The median sensitivity was 91% (range 73-97%), the median specificity was 90% (range 73-97%), the median positive LR was 9.1 (range 1.54 to infinity) and the median negative LR was 0.14 (range 0.04 to 0.37).

Nine studies used a cut-off point of 30 mg/mmol. In comparison with 24-hour urine collection, pooled results showed sensitivity of 83.6% (95% CI 77.5% to 89.7%), specificity of 76.3% (95% CI 72.6% to 80.0%), positive LR of 3.53 (95% CI 2.83 to 4.49) and negative LR of 0.21 (95% CI 0.13 to 0.31; n=1,003 women).

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 to 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 negative LR of 0.05 compared to 24-hour albuminuria.

Evidence statement

One systematic review⁸⁶ [EL=Ib] assessed the accuracy of the spot protein:creatinine ratio and spot albumin:creatinine ratio compared with 24-hour urine collection for the detection of significant proteinuria in hypertensive pregnant women. The results are summarised in Table 5.2.

Table 5.2 Summary of Cote et al's (2008) systematic review⁸⁶

Ratio investigated	Study characteristics	Results
Spot protein:creatinine ratio	11 studies with 8 cut off points: (median 24 mg/mmol; 17-57 mg/mmol)	
	Sensitivity Specificity	Median 84% (range 78-90%) Median 76% (range 73-80%)

	(+) LR (-) LR	Median 3.53 (range 2.83 to 4.49) Median 0.21 (range 0.13 to 0.31)
	Cut-off: 30 mg/mmol (9 studies; 1003 women)	
	Sensitivity Specificity (+) LR (-) LR	83.6% (77.5% to 89.7%) 76.3% (72.6% to 80.0%) 3.53 (2.83 to 4.49) 0.21 (0.13 to 0.31)
Spot albumin: creatinine ratio	Cut-off: 2 mg/mmol	
	Sensitivity Specificity (+) LR (-) LR	94% 94% 15.7 0.06
	Cut-off: 27 mg/mmol	
	Sensitivity Specificity (+) LR (-) LR	95% 100% infinity 0.05

GDG interpretation of the evidence

The GDG recognised the considerable variations that existed in the study populations, designs and quality. Visual urinary dipstick testing is a poor test for the diagnosis of pre-eclampsia and a protein-negative result on dipstick testing does not exclude significant proteinuria (>300mg/24h). Higher thresholds of dipstick testing have higher specificity and higher positive LR, but at a cut-off of 1+ visual dipstick testing has a sensitivity of 55% and a specificity of 84%. Automated dipstick testing improves test performance with a sensitivity of 82% and specificity of 81% using a 1+ threshold and appears to be cost saving.

The evidence for the use of spot protein:creatinine and albumin:creatinine ratios looks promising but there were significant variations within the study designs which made the results difficult to interpret. Standardisation of the protein:creatinine ratio to 30mg/mmol showed a test performance virtually identical to that of automated dipsticks (sensitivity 83.6%, specificity 76.3%). The GDG's view is that these tests are not yet suitable for routine use.

Although it is clinically inconvenient to have to collect urine for 24 hours to establish the amount of protein excreted there was insufficient evidence to be able to recommend the use of a shorter collection period.

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

Recommendations

Use an automated dipstick for measuring proteinuria to diagnose pre-eclampsia in a secondary care setting.

Use 24-hour urine collection to quantify proteinuria if there is 1+ or more on automated urinary dipstick.

Research recommendations

What is the best method to assess the presence and amount of proteinuria in women with new hypertension during pregnancy?

Why this is important

Most of the adverse outcomes of hypertension during pregnancy occur in women with pre-eclampsia. The test to determine the diagnosis is the key test in any assessment of new hypertension. Current use of dipsticks and 24-hour urine

collection is challenged by modern near patient testing and by a lack of association between values traditionally regarded as abnormal and clinical outcomes.

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. Section 5 has dealt with how to distinguish between those with significant proteinuria and those without. This section 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 i.e. pre-eclampsia or those with underlying pathology.

6.2 Frequency of blood pressure measurement

No studies were found which provided 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 62.²⁴

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. [EL=2+] ⁸⁷ The retrospective analysis (n=661) included women initially diagnosed as having gestational hypertension, and the prospective study (n=184) 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 \geq 300 mg/day (or persistently \geq 2+ on dipstick urinalysis), renal impairment (plasma creatinine \geq 100 μ mol/L), hepatic dysfunction (aspartate aminotransferase \geq 50

IU/L and or severe persistent epigastric pain), haematological abnormalities (haemolysis and /or platelet count $< 150 \times 10^9/l$), cerebral disorder (visual scotomata, convulsions, hyper-reflexia when accompanied by clonus) or severe hypertension (BP ≥ 170 mmHg and or diastolic BP > 110 mmHg). Eclamptic women were included in the pre-eclampsia group.

In the univariate analysis of the combined data the following predictors were shown to be 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 did not show 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.⁸⁸ [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 and tobacco use between those with and those without proteinuria. Gestational age at enrolment ($p= 0.004$; OR 0.92, 0.88-0.97) and maternal age ($p= 0.028$; OR 0.97, 0.94-1.00) were significant predictors of proteinuria. BMI ($p= 0.091$; OR 1.02, 1.00-1.04), parity ($p= 0.143$; OR 1.30, 0.91-1.84), history of miscarriage ($p= 0.953$; OR 0.99, 0.61-1.60), systolic blood pressure ($p= 0.891$; OR 1.00, 0.98-1.01) and diastolic blood pressure ($p= 0.747$; OR 1.00, 0.98-1.02) were not significant predictors of proteinuria.

One case-control study conducted in the UK studied 560 women with suspected gestational hypertension.⁸⁹ [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_s (LR₊ 1.80, 1.5-2.2; LR₋ 0.64, 0.5-0.8).

Evidence statement

Three studies investigated the effect of gestational age at diagnosis and progression from gestational hypertension to pre-eclampsia. These showed a 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 are 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 ($p= 0.004$; OR 0.92, 0.88-0.97) and maternal age ($p= 0.028$; OR 0.97,

0.94-1.00) were significant predictors of proteinuria. BMI, parity, history of miscarriage, systolic blood pressure and diastolic blood pressure were not found to be significant predictors of proteinuria.

One case-control study [EL II] looked at the ability of different 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%, specificity of 69% and LRs.

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

Serum uric acid

One study [EL II] and two studies [EL=III] investigated the predictive value of serum uric acid using different reference standards.^{85;89;90}

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.⁸⁵ [EL=III] The included women were between 28-30 weeks gestation and had less than 0.3g protein in a 24-hour urine sample at the time of sampling. No exclusion criteria were stated. Whether the first morning urine void was excluded from the 24-hour collection has not been reported. The timing of the tests, and whether outcome assessors were blinded to the results was not reported. Serum uric acid levels have been compared to 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/l. Sensitivity, specificity, 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.⁹⁰ [EL=III] The study population (n=325) consisted of women referred to the antenatal day unit between March 1992 and end of July 1993 with a diagnosis of mild hypertension (defined as diastolic blood pressure of ≥ 90 mmHg 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/l in primigravid women (n=168) in predicting proteinuria was 7.7% (95% CI 3.0% to 18.2%), the specificity 95.5% (95% CI 89.9% to 98.1%), the positive and, again, the negative LRs were poor. Using a threshold of 0.35 mmol/l gives 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 multi-gravid women (n=157).

Anumba et al.⁸⁹ [EL II] showed that uric acid had a sensitivity of 65% in predicting pre-eclampsia in women with suspected gestational hypertension. It also has 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/l, the sensitivity was 65%, specificity 47% with LRs (LR+ 1.24, 1.01-1.5; LR- 0.74, 0.5-1.0).

Evidence statement

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 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 lowers the results slightly and leads to a sensitivity of 21% and a specificity of 87% in primigravid women. The results

are 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 significant LRs (LR+ 1.24, 1.01-1.5; LR- 0.74, 0.5-1.0).

Platelet count

A study which investigated the predictive value of the platelet count has been conducted in the UK including 325 women with gestational hypertension.⁹⁰[EL=III] All women referred to the antenatal day unit between March 1992 and end of July 1993 with a diagnosis of mild hypertension defined as diastolic blood pressure of ≥ 90 mmHg 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 $150 \times 10^9/l$ were 9.8% (95% CI 4.3% to 21%) and 92.3% (95% CI 86% to 95.9%) 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%) in multigravid women (n=157). The LRs were poor. Using a threshold of $200 \times 10^9/l$ 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 are similar in multigravid women.

Anumba et al.⁸⁹ [EL II] showed that platelet count is not a significant predictor of pre-eclampsia in women suspected of having gestational hypertension.

Evidence statement

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 $150 \times 10^9/l$ the sensitivity was below 10% although specificity was 92%. Using a higher threshold ($200 \times 10^9/l$) resulted in poor sensitivity (45%) and poor specificity (62%).

The second study could not demonstrate a relationship between maternal platelet count at diagnosis and subsequent pre-eclampsia or fetal growth restriction.

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 platelet measure is not a 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 regime (PET) among women with gestational hypertension. Pre-eclampsia regime was defined as the need for intravenous antihypertensive therapy and anticonvulsant.⁹⁰

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

Sensitivity and specificity for a platelet count below $150 \times 10^9/l$ for predicting PET 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 LR were 3.83 (1.05 to 13.95) and 0.77 (0.48 to 1.24) respectively. The sensitivity, specificity, positive and negative LR for a platelet count below $200 \times 10^9/l$ were 50% (18.8% to 81.2%), 53.6% (45.7% to 61.4%), 1.08 (0.48 to 2.45) and 0.93 (0.41 to 2.10) in primigravid women respectively.

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

Evidence statement

One study investigated the effectiveness of platelet count and serum uric acid for predicting PET among women with gestational hypertension. Using the threshold $150 \times 10^9/l$, the sensitivity for platelet count was very poor (29%), while specificity was very high (94%). Using a threshold of $200 \times 10^9/l$ gives 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/l and 0.35 mmol/l thresholds.

Urea and serum creatinine

Anumba et al. ⁸⁹ [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 LR (LR+ 1.23, 1.0-1.5; LR- 0.76, 0.6-1.0).

Liver function tests

Anumba et al. ⁸⁹ [EL II]) showed that in women suspected of having gestational hypertension alanine aminotransferase (ALT) measure was not a significant predictor of pre-eclampsia.

No evidence was found for coagulation and clotting tests.

Blood pressure

Anumba et al. ⁸⁹ [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 significant LR (LR+ 1.85, 1.6-2.3; LR- 0.55, 0.4-0.8) 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 significant LR (LR+ 1.4, 1.1-1.6; LR- 0.69, 0.5-0.9). Diastolic blood pressure had a sensitivity of 45% and specificity of 80% with significant LR (LR+ 2.33, 1.8-2.9; LR- 0.68, 0.5-0.9) 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 significant LR (LR+ 1.18, 1.0-1.4; LR- 0.44, 0.2-0.8).

Evidence statement

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 systolic blood pressure had a sensitivity of 62-64%, specificity of 54-65% (depending on the predictive value used) and LR. Diastolic blood pressure had a sensitivity of 45-89%, specificity of 24-80% and significant LR.

Cost effectiveness

There were no economic evaluations that considered the cost-effectiveness of the different 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 or severe hypertension respectively. See the table on women with new-onset hypertension and no proteinuria and the one on women with new-onset hypertension with proteinuria in the recommendations 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 cerebrovascular accident (stroke) 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 of differing care by gestation at presentation difficult. The UK study's finding of an association between gestation at presentation and fetal growth restriction 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 al⁸⁹ 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 were not good at predicting pre-eclampsia the GDG feels that a negative test was also an important finding as it would indicate non-progression of the disease process.

In spite of the poor evidence base the GDG felt 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.

6.4 Prevention of pre-eclampsia

Clinical effectiveness

Anti-platelet 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.⁹¹[EL=1+] The study population consisted of 47 nulliparous women between 30-36 weeks gestation and a diagnosis of mild pregnancy-induced hypertension (defined as a systolic blood pressure between >140 and <165 mmHg and/or diastolic blood pressure >90 but <110 mmHg, on at least two occasions at least 6 hours apart and no signs of moderate to severe pregnancy-induced hypertension such as a low platelet count (less than 105) or proteinuria of more than 500mg/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. 23 women were randomly allocated to receive 100mg aspirin per 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 (6/23 versus 6/24, RR=1.04, 95% CI 0.39 to 2.77), gestational age at delivery, newborn weight, newborn percentile, and 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 to placebo or no treatment.³⁹ [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 to placebo or no treatment.

GDG interpretation of the evidence

The GDG does not consider 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,⁹² 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 appears to be a mixture of women with gestational and chronic hypertension or where the exact nature of the hypertensive disorder is 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).⁹³⁻⁹⁶ [EL=1-] One trial reported that statistically significantly fewer women taking labetalol developed severe hypertension compared to women taking placebo (RR=0.35, 95% CI 0.14 to 0.92).^{93,94} The other trial reported no statistically significant effects for any of the maternal or fetal outcomes.^{95,96}

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

Two studies investigated the effectiveness of beta-blocker compared with placebo.^{97,98} [EL=1-] One study⁹⁷ found that among women who received atenolol, fewer were admitted to hospital before giving birth compared to women who received no treatment (RR=0.41; 95% CI 0.27 to 0.62). The other study⁹⁸ investigated the effectiveness of beta-blocker 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 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 to women who received methyldopa (RR=0.04, 95% CI 0.003 to 0.73).⁹⁹[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) versus no specific treatment or late treatment (after 28 weeks gestation).¹⁰⁰[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 were split into treatment and no treatment groups. That 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 eight days longer gestation than women who did not receive treatment (late control: 264 days \pm 13 and late treated 272 days \pm 11). No statistically significant differences were found between treatment and control group (early and late) for proteinuria (>

100mg/dl), mean birth weight, increase in plasma urate, oedema scores or weight gain.

Further results from the same study described above are reported in another publication.⁷⁸ Combining the late treatment with the early treatment group and comparing this to the combined late and early control group, the study found that the incidence of the maximum diastolic blood pressure ≥ 110 mmHg to be lower in the treated women, compared to 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 (56% of controls and 58% of treatment 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 study¹⁰¹ 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 study¹⁰² investigated the effectiveness of hydralazine compared to 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^{103;104} investigated labetalol versus methyldopa and one study¹⁰⁵ 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^{106;107} compared beta-blockers with placebo. The study which investigated the beta-blocker metoprolol did not show any statistically significant results. The other study¹⁰⁷ showed that fewer women developed severe hypertension when given pindolol when compared to women who received a placebo.

One small (n=51) low quality study compared the beta-blocker atenolol with the beta-blocker pindolol.¹⁰⁸ [EL=1-] The only outcome of interest reported was severe hypertension which was not statistically significant (Table 6.2b).

Beta blockers and methyldopa

Five studies¹⁰⁹⁻¹¹⁴ 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-blocker 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 metoprolol.¹¹⁵[EL=1-] 100 women with singleton pregnancies and mild or moderate hypertension and were at least 20 weeks pregnant were included in the study. Hypertension was defined as systolic blood pressure of ≥ 140 mmHg and/or a diastolic blood pressure of ≥ 90 mmHg. None of the included women had received other antihypertensive medication before entry to the study. 50 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 nifedipine showed to have a statistically significantly lower systolic and diastolic blood pressure compared to 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 includes 7 studies. For the outcomes, severe hypertension (n=3 studies), perinatal mortality (n=6 studies), proteinuria at delivery (n=5 studies), admission to special care baby unit (n=2 studies) no statistical significant results were found. Due 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/ITU and small for gestational age.

Calcium channel agents and methyldopa

An RCT conducted in Sri Lanka compared the effectiveness of nifedipine with methyldopa.¹¹⁶[EL=1-] A total of 126 women were included. The inclusion criteria were systolic blood pressure \geq 140 mmHg, a diastolic blood pressure of \geq 90 mmHg on two occasions 12 hours apart, normal blood pressure before pregnancy, being normotensive at booking and no previous history of renal, vascular and collagen disease. Selected women were alternately allocated to receive either 30mg to 90mg nifedipine per day or 750 to 2000 mg methyldopa.

Apgar score was better for infants of women who received methyldopa. More women needed treatment for acute hypertension in the nifedipine group compared to 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 abruptio placentae, HELLP syndrome, eclampsia, caesarean section, maternal side effects, birth weight, intrauterine death and maturity at delivery.

1 Table 6.1a Results for women with gestational hypertension – intervention compared to placebo (reported as RRs or ORs with 95% CIs)

Study [Evidence Levels]	Severe hypertension	Pre-eclampsia/Proteinuria	Eclampsia/HELLP	Maternal death	Admission to HDU/ITU	Perinatal mortality	Small-for-gestational age	Preterm birth	Admission to neonatal unit
<i>Labetalol versus placebo</i>									
Pickles ^{93,94} 1989, 1992 [EL=1-] Country: 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)
Cruikshank ^{95,96} 1991, 1992 [EL=1-] Country: 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)
<i>Beta-blocker versus placebo</i>									
Rubin ⁹⁷ 1983 (Atenolol) [EL=1-] Country: 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 ⁹⁸ 1990 (Oxprenolol) [EL=1-] Country: 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)

2
3

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

Study [Evidence Levels]	Severe hypertension	Pre-eclampsia/Proteinuria	Eclampsia/HELLP	Maternal death	Admission to HDU/ITU	Perinatal mortality	Small-for-gestational age	Preterm birth	Admission to neonatal unit
<i>Labetalol versus methyldopa</i>									
El-Qarmalawi ⁹⁹ 1994 [EL=1-] Country: 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	-
<i>Bed-rest versus normal activities at home</i>									
Crowther ⁷² 1992 [EL=1+] Country: Australia	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)	-	-

2 ^a Preterm labour

3

4 The results from mixed studies give other information but are very varied in their conduct and their recruitment (see Tables 6.2a and 6.2b).

5

6 Table 6.2a Results for mixed populations – intervention compared to placebo (reported as RRs or ORs with 95% CIs)

Study [Evidence Levels]	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP	Maternal death	Admission to HDU/ITU	Perinatal mortality	Small-for-gestational age	Preterm birth	Admission to neonatal unit
<i>Beta-blocker versus placebo</i>									
Wichman ¹⁰⁶ 1984 (Metoprolol) [EL=1-] Country: 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 ¹⁰⁷ 1992 (pindolol) [EL=1-]	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	-	-	-

Country: Israel						28.73)			
<i>Methyldopa versus no specific treatment</i>									
Redman ^{100,78} 1976 [EL=1-]	-	Not significant	-	-	-	-	-	-	-
Country: UK									
<i>Metoprolol plus hydralazine versus no treatment</i>									
Högstedt ¹⁰¹ 1985 [EL=1-]	-	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)	-
Country: Sweden									

1

2

Table 6.2b Results for mixed populations – comparison between two interventions or no intervention (reported as RRs or ORs with 95% CIs)

Study [Evidence Levels]	Severe hypertension	Pre-eclampsia/proteinuria	Eclampsia/HELLP	Maternal death	Admission to HDU/ITU	Perinatal mortality	Small-for-gestational age	Preterm birth	Admission to neonatal unit
<i>Labetalol versus methyldopa</i>									
Redman ⁷⁸ 1977 [EL=1-]	-	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)
Country: UK and Ireland									
Lamming ¹⁰³ 1980 [EL=1-]	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	-	-	-
Country: UK									
Plouin ¹⁰⁴ 1988 [EL=1-]	-	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)
Country: France									
<i>Hydralazine versus hydralazine plus propranolol or pindolol</i>									
Paran ¹⁰² 1995 [EL=1-]	-	-	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	-
Country: Israel									

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								4.35)	
<i>Labetalol versus hydralazine</i>									
Hjertberg ¹⁰⁵ 1993 [EL=1-] Country: 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)	-	-
<i>Beta-blocker versus beta-blocker</i>									
Tuimala ¹⁰⁸ 1988 (Atenolol versus Pindolol) [EL=1-] Country: Finland	3/24 versus 4/27 RR=0.84 (0.21 – 3.40)	-	-	-	-	-	-	-	-
<i>Beta-blocker versus methyldopa</i>									
Fidler ¹⁰⁹ 1983 (Oxprenolol) [EL=1-] Country: 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 ^{110,111} 1979 (Oxprenolol) [EL=1-] Country: 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 ¹¹² 1992 (Metoprolol) [EL=1-] Country: 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 ¹¹⁷ 1983 (Propranolol) [EL=1-] Country: 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 ¹¹⁴ 1986 (Pindolol) [EL=1-]	-	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	-	-	-

Country: Israel						(0.07 to 14.64)			
<i>Beta-blocker versus nicardipine</i>									
Jannet ¹¹⁵ 1994 (Metoprolol) [EL=1-]	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)
Country: France									
<i>Calcium-channel blocker verapamil versus beta-blocker</i>									
Marlettini ¹¹⁸ 1990 (Pindolol) [EL=1-]	-	-	-	-	-	0/22 versus 0/22 not estimable	-	-	-
Marlettini ¹¹⁸ 1990 (Atenolol) [EL=1-]	-	-	-	-	-	0/25 versus 0/25 not estimable	-	-	-
Country: Italy									
<i>Calcium-channel blocker versus methyldopa</i>									
Jaryawardana ¹¹⁶ 1994 (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 – 15.64) ^b	-	-	-	-	-	-

1 ^a The outcome reported was need for treatment for acute hypertension

2 ^b The outcome reported was HELLP syndrome

3

Evidence statement

In the majority of included studies examining the effect of antihypertensive agents (n=18) the population was either not clearly defined or included a mixed population, with various combinations of women with and without proteinuria, women with gestational hypertension and/or with chronic hypertension.

Overall, 7 studies^{72;91;93;94;97-99;119;120} were included for women with gestational hypertension alone. No suitable studies were identified for antihypertensive treatment such as methyldopa, prazosine and hydralazine, for calcium channel blocker or for diuretics. Five small studies [EL=1-] investigated the effectiveness of alpha- and beta-blockers. One study⁹⁹ found labetalol to lower the incidence of severe hypertension compared to placebo, whereas another⁹⁷ found beta-blocker to lower the rate of hospital admission before birth compared to placebo. One quasi-randomised study⁹¹ found labetalol to lower the incidence of pre-eclampsia compared to 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 which compared labetalol with hydralazine did not show any statistically significant result. Two studies investigated beta-blocker 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 with nicardipine and one study with another beta-blocker. One study compared metoprolol plus hydralazine with no treatment and another study hydralazine with hydralazine combined with propanolol or with pindolol. Furthermore, one study compared verapamil with two different beta-blockers and another study methyldopa with no specific treatment. None of these studies achieved any statistically significant results. One study found nifedipine 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.⁷² [EL=1+] Two hundred and eighteen women with singleton pregnancies with blood pressure $\geq 140/90$ mmHg, without proteinuria and between 28 and 38 weeks gestation were included in this study. Women who were symptomatic, had a diastolic blood pressure ≥ 100 mmHg, 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 and normal activities at home 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 218 women (including those with chronic hypertension) hospital admission for bed rest decreased the risk of preterm delivery 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 delivery <34 weeks,

development of proteinuria or severe proteinuria, incidence of SGA babies and admission to a neonatal unit).

Evidence statement

A small but well conducted RCT [EL=1+] conducted in Zimbabwe found hospital bed rest compared to 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 to 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 stroke 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 strokes 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 was 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 which 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: <ul style="list-style-type: none"> • diastolic blood pressure less than 80–100 mmHg • systolic blood pressure less than 150 mmHg 	With oral labetalol† as first-line treatment to keep <ul style="list-style-type: none"> • diastolic blood pressure less than 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 dipsticks	At each visit using automated dipsticks	Daily using automated dipsticks

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: <ul style="list-style-type: none"> • kidney function, electrolytes, full blood count, transaminases, bilirubin
-------------	---------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------

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 recommendations

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 examination fetal surveillance in a population that only includes women with gestational hypertension and therefore inference on surveillance must 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 evidence that early onset gestational hypertension carries an increased risk of fetal growth restriction and the GDG feels that it would be reasonable to consider biometry in this group.

Although the single study on umbilical artery Doppler that deals with hypertensive pregnancies appeared to show no benefit to the use of umbilical artery Doppler velocimetry, 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 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 outside the preterm group.

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 (refer ANC). 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 pool – 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 they recommend 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 Section 7).

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

6.7 Timing of birth

Clinical effectiveness

One multicentre, open-label RCT,¹²¹ [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 (n= 379) group. 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 induction of labour group (88 (23%) versus 138 (36%), RR 0.64, 95% CI 0.51 to 0.80), and a statistically significantly lower risk of severe hypertension in the induction of labour group (for systolic BP, 55 (15%) versus 88 (32%), RR 0.63, 95% CI 0.46 to 0.86; for diastolic BP, 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 (5-minute Apgar score < 7, umbilical artery pH <7.05 or admission to neonatal intensive care unit), 5-minute Apgar score < 7, admission to intensive care, duration of stay in neonatal intensive, high or medium care unit). However, umbilical artery pH < 7.05 occurred statistically significantly less frequently in babies of women in the induction of labour group (9 (3%) versus 19 (6%), 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 versus 3490, IQR 2570 to 4235, $p < 0.0001$, CI not reported), but this was 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 was no statistically significant difference 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 gestational hypertension (31 (13%) versus 42 (17%), RR 0.76, 95% CI 0.50 to 1.17).

Evidence statement

One RCT¹²¹ [EL 1+] showed that induction of labour in women with gestational hypertension or mild pre-eclampsia significantly lowered the risks of progression to severe hypertension compared to 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 gestational hypertension and 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 trial¹²¹ we constructed a decision tree 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 to 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 to expectant management. The mean cost per woman for immediate birth was estimated to be £2,774 compared to £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. Using univariate sensitivity analysis we showed that the base-case results were robust to changes in model assumptions except changes in the incidence of severe disease.

GDG interpretation of the evidence

The HYPITAT trial¹²¹ combined mild pre-eclampsia (as defined in this guideline) and mild gestational hypertension (defined as diastolic blood pressure ≥ 95 mmHg compared with ≥ 90 mmHg 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 are 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 shows a trend to better maternal outcomes (less development of severe hypertension), but the difference is 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 to 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 anti-hypertensive 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 trial¹²¹ are not directly applicable to the UK clinical setting because in the Netherlands gestational hypertension is managed by offering immediate birth without anti-hypertensive treatment. However, the GDG's view is that if gestational hypertension becomes severe ($\geq 160/110$ mmHg), even with anti-hypertensive treatment, then the woman should be offered immediate birth after a course of antenatal steroids 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 antenatal steroids (if required) has been completed.

6.8 Postnatal investigation, monitoring and treatment

Clinical effectiveness

A single literature search was conducted for the different 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 1,979 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 [EL 1-]¹²² compared the use of timolol and methyldopa in the management of puerperal hypertension. Untreated postpartum women with diastolic blood pressure (95-105 mmHg) were randomly allocated to either receive timolol (n=40) (5mg orally, 3 times a day) or methyldopa (n=40) (250 mg orally, 3 times a day). In both cases, the dose was doubled every 24 hours twice if diastolic blood pressure was > 95 mmHg. Antenatally, 46 of the 80 women had received drug treatment for hypertension and another 14 had had mild hypertension (<95 mmHg) which did not require treatment. The remaining 20 women were not 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 significant difference in the number of those who had their medications changed due 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 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 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 34.²⁹

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 did not take antihypertensive treatment and have given birth, aim to keep blood pressure lower than 140/90 mmHg.

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.

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 prior to 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 review¹²³ [EL=Ib] 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. The review included sixteen diagnostic studies (n= 6,749 women with pre-eclampsia) looking at the use of only urine dipstick (5 studies), only laboratory method (8 studies), either dipstick or laboratory method (2 studies) or only the protein: creatinine ratio (1 study) to assess maternal or fetal complications. Studies were considered to be of good quality if they used prospective design (5 studies), consecutive enrolment (6 studies), and full verification of the test result with reference standard (16 studies) and had adequate test description (10 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= 7,066) found there was an increased likelihood of stillbirth with proteinuria, and a decreased likelihood of stillbirth in the absence of proteinuria [5g/24hr three studies, n= 546, LR+ 2.0 (1.5-2.7), LR- 0.53 (0.27-1); 1+

one study, n= 3,260, LR+ 1.3 (1.2-1.4), LR- 0.69 (0.59-0.82); 3+ one study, n= 3,260, LR+ 2.3 (1.9-2.7), LR- 0.76 (0.70-0.84)]. Four studies (n= 888) out of seven studies (n= 1,180) had significant findings that there was an increased likelihood of a small for gestational age baby in the presence of proteinuria and a decreased likelihood in the absence of proteinuria [2+ one study, n= 307, LR+ 1.3 (1.1-1.5), LR- 0.45 (0.21-0.96); 3+ two studies, n= 386, LR+ 1.6 (1.1-2.3), LR- 0.75 (0.59-0.96); 0.5g/24hr one study, n= 195, LR+ 1.7 (1.1-2.7), LR- 0.73 (0.52-1.0)]. No significant LRs for small for gestational age were found at a proteinuria cut off of 1+ (1 study, n=87), 0.3g/24hr (1 study, n= 195) or 5g/24hr (1 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 decreased likelihood of NICU admission in the absence of proteinuria [5g/24hr two studies, n= 316, LR+ 1.5 (1.0-2.0), LR- 0.78 (0.64-0.95); 10g/24hr one study, n= 209, LR+ 5.6 (1.8-17.4), LR- 0.77 (0.69-0.87)]. No significant LRs for NICU admission were found for cut offs of 1+ (1 study, n= 87) or increase by 2g/24hr (1 study, n= 340). One study (n= 209) out of three studies (n= 492) found a significant increase in likelihood of eclampsia in the presence of proteinuria (10g/24hr; LR+ 2.7, 1.1-6.2). However, at the same level of proteinuria there was no decrease in likelihood of eclampsia in the absence of proteinuria, and no significant LRs were found at a cut off of 5g/24hr (1 study, n= 209) or increase by 2g/24hr (1 study, n= 74). One study (n= 321) out of three studies (n= 1,079) found a significant increase in likelihood for perinatal death in the presence of proteinuria (500 mg/mmol; LR+ 5.3, 1.3-22.1). However, no significant decrease in likelihood was found at the same cut off, and no significant LRs were found at a cut off of 1g/l (1 study, n= 379) or 2g/l (1 study, n= 379). There was no significant findings for the likelihood of placental abruption (3 studies, n= 247), HELLP syndrome (4 studies, n= 558) or neonatal death (5 studies, n= 698) in the presence of absence of proteinuria. The study concludes 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 small for gestational age were found in the majority of studies, and for NICU admission in half of the studies but LRs were in the values regarded as of little predictive use. One study reported a significant but weak positive LR for eclampsia and another for perinatal death, but no other 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 view is that once the diagnosis of significant proteinuria has been made there is little benefit from repeating the analysis.

7.4 Biochemical tests

Clinical effectiveness

Uric acid

A systematic review of 18 primary articles, comprising 41 studies and 3913 women with pre-eclampsia, has been conducted to evaluate the effectiveness of maternal serum uric acid in predicting maternal and fetal outcome. [EL=III] ¹²⁴ 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 effect model was used for pooling the individual studies.

The overall pooled positive and negative LRs for serum uric acid (3 studies, n=634) for predicting eclampsia, using the threshold of 350 micromol/l, 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 6 studies and 1583 women. Only one study (n=194) had HELLP syndrome as an outcome. The positive and negative LRs for 450 µmol/l 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 µmol/l.

Fetal outcomes included small for gestational age, 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 a small for gestational age infant. Five studies (n=1219) were included for these pooled estimates. For predicting stillbirth and neonatal death 4 studies (n=1040) were included in the meta analysis and the pooled LRs were 1.5 (95% CI 0.91 to 2.6) positive and 0.51 (95% CI 0.20 to 1.3) negative LR. 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 µmol/l and had a LR+ of 2.7 (0.71 to 9.8) and a LR- of 0.13 (0.01 to 2.4). Another study (n=200) used a threshold of 330 µmol/l and obtained positive and negative LRs of 2.8 (0.42 to 18.3) and 0.28 (0.01 to 5.9) respectively. The study using a threshold of 350 µmol/l (n=103) had a LR+ of 2.1 (0.89 to 5.1) and LR- of 0.07 (0.01 to 1.3) and the study using a threshold of 520 µmol/l (n=229) obtained a LR+ of 1.5 (0.40 to 5.3) and a LR- of 0.93 (0.46 to 1.9). Subgroup analysis was undertaken for different severity levels of preeclampsia and different thresholds. The results of the subgroup analyses did essentially not differ 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-significant LRs. Serum uric acid seem to be weakly effective in predicting small for gestational age (pooled LR+=1.3, LR-=0.60) but not for predicting stillbirths and neonatal deaths. The pooled LRs for stillbirth and neonatal deaths were not statistically significant. Four individual studies on serum uric acid for predicting intrauterine death were all non-significant.

Renal function tests, platelets and liver function

A retrospective observational study, including 111 women with pre-eclampsia, has been conducted in Sweden to identify risk factors predicting maternal or fetal complications.¹²⁵ [EL=2+] Of the included women, 70 had mild pre-eclampsia and 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 \geq 140/90 mmHg together with albuminuria of at least 300 mg/24hours after 20 weeks gestation. Severe pre-eclampsia was defined according to American College of Obstetricians and Gynaecologists (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 <0.140 in the univariate analysis were entered into a multivariate model which gave adjusted ORs. The ORs for each variable was related to a unit change for that variable e.g. a blood pressure change of 1 mmHg and change of 1g for 24 hour albumin excretion. One unit change in ALT represented a change of 0.1 μ kat/l. Maternal complications were defined as eclampsia, placental abruption, and oliguria (urine production <600ml/24hours), and HELLP syndrome (LDH>8 μ kat/l, ALT >70, and platelet count <150x10⁹/l).

Significant ORs for maternal complications in the univariate analysis were systolic (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 significant OR (OR=1.31; 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 non-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 significant. None of the following variables was predictive for giving birth to a small for gestational age infant: creatinine, uric acid, albumin, haemoglobin, platelets, ALT, albumin excretion, and systolic and diastolic blood pressure. None of these associations became significant after adjustment for confounders. Variables predictive for admittance to the neonatal intensive care unit were ALT (OR=1.13; 95% CI 1.01 to 1.26), and systolic (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 significant in the univariate analysis but disappeared after adjustment for confounding variables. Creatinine, uric acid, albumin, haemoglobin, platelets, and albumin excretion were not significantly associated with admittance to the neonatal intensive care unit.

One cohort study¹²⁶ [EL= 2+] was conducted in Canada, New Zealand, the UK and Australia. It looked at 737 women with hypertension and proteinuria (n= 464), hypertension and hyperuricaemia (n= 116), HELLP without hypertension or proteinuria (n= 30) or superimposed pre-eclampsia (n= 127). The study compared factors measured at presentation of illness to 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 significant association between adverse maternal and perinatal outcomes and platelets below 100 x 10⁹/l (n= 53 /735, p= 0.001 and p= 0.013 respectively). There was a significant association between adverse maternal outcomes, but not adverse perinatal outcomes, and elevated liver enzymes (n= 352/737, p= <0.001 and p= 0.868 respectively), creatinine greater than 110 μ M (n= 18/734, p= <0.001 and p= 1.000 respectively), increased AST and/or ALT (n= 183/737, p= 0.006 and p= 0.085 respectively) and increased LDH or microangiopathic haemolytic anaemia (n= 292/698, p= 0.001 and p= 0.374 respectively).

There was no significant association between adverse maternal or perinatal outcomes and serum albumin less than 18 g/L (n= 11 /652, p= 0.328 and p= 0.438 respectively) or proteinuria of greater than or equal to 2+ (n= 445 /726, 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 significantly associated with maternal complications in the univariate analysis. After adjustment, ORs

remained significant only for diastolic blood pressure (OR=1.13; 95% CI 1.01 – 1.25). Creatinine, uric acid and albumin did not prove to be significantly associated with maternal outcomes. None of the nine factors investigated (creatinine, uric acid, albumin, haemoglobin, platelets, ALT, albumin excretion, systolic and diastolic blood pressure) were associated with giving birth to a small for gestational age infant. Univariate analysis showed that systolic and diastolic blood pressure and ALT were associated with referral to neonatal intensive care unit.

A case-control study showed an association between a platelet count less than 100×10^9 per litre, elevated transaminases and creatinine more than 110 microMol 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 believe 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 and moderate new-onset hypertension and proteinuria whilst an inpatient.

The risk of cerebrovascular accident (stroke) 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 are the weak association between more than 5g proteinuria per 24 hours and stillbirth, admission to NICU and small for gestation. Likelihood ratios are 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 is 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 $>100 \times 10^9/l$.

7.5 Treatment of hypertension

Clinical effectiveness

The data are summarised in Tables 7.1 (women with pre-eclampsia) and 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.¹²⁷ [EL=1+] Statistically significantly fewer women developed severe hypertension when they were treated with labetalol compared to 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.

Table 7.1a Results for women with pre-eclampsia – intervention compared to no treatment (reported as RRs or ORs with 95% CIs)

Study [Evidence Levels]	Severe hypertension	Pre-eclampsia/Proteinuria	Eclampsia/HELLP	Maternal death	Admission to HDU/ITU	Perinatal mortality	Small-for-gestational age	Preterm birth	Admission to neonatal unit
<i>Labetalol versus no treatment (all study participants were inpatients)</i>									
Sibai ¹²⁷ 1987 [EL=1+] Country: 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)
<i>Methyldopa versus no treatment (all study participants were inpatients)</i>									
Elhassan ¹²⁸ 2002 [EL=1-] Country: 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

a Severe pre-eclampsia >5 g/24 hours

b Referral to a paediatrician

Table 7.1b Results for women with pre-eclampsia – comparison of two interventions (reported as RRs or ORs with 95% CIs)

Study [Evidence Levels]	Severe hypertension	Pre-eclampsia/Proteinuria	Eclampsia/HELLP	Maternal death	Admission to HDU/ITU	Perinatal mortality	Small-for-gestational age	Preterm birth	Admission to neonatal unit
<i>Methyldopa versus isradipine (all study participants were inpatients)</i>									
Montan ¹²⁹ 1996 [EL=1-] ^a Country: Singapore	-	-	-	-	-	-	-	-	-
<i>Nifedipine and bed rest versus bed rest alone</i>									
Sibai ¹³⁰ 1992 [EL=1+]	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	49/99 versus 41/101 RR=1.23	30/99 versus 21/101 RR=1.46 (0.90 to 2.36)

Country: USA							2.35) ^d	(0.88 to 1.70)	
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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

Methyldopa

Two trials investigated the effectiveness of methyldopa, one study¹²⁸ compared it with no treatment and one with the calcium-channel blocker isradipine¹²⁹. Both studies are of evidence level [EL=1-].

In addition some of the mixed trials presented in section 6 include women with pre-eclampsia.

An RCT conducted in Sudan compared methyldopa with no drug treatment.¹²⁸ [EL=1-] Women were included if they had a singleton pregnancy between 28-36 weeks gestation, a diastolic blood pressure between 90 and 109 mmHg in two readings six hours apart, and $\geq 2+$ albumin on dipstick. 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 methyldopa was given and gradually increased to a maximum of 4 gm. 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.

Converting the reported incidence figures into relative risks, showed that women receiving methyldopa were considerably less likely to develop severe pre-eclampsia compared to 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, and referral of the baby to a paediatrician, gestational age at delivery, birth weight and Apgar score less than 7 at 5 minutes.

A very small, low quality RCT was conducted in Singapore comparing methyldopa with isradipine.¹²⁹ [EL=1-] Women with pre-eclampsia (n=27) received either 250mg methyldopa three times a day (n=10) or 2.5mg 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 birth weight was 2648g in the methyldopa group (SD 510g) and 2866g (SD 428g) in the isradipine group (two-tailed p calculated by t-test from the reported means and SD: p=0.30). One woman had a caesarean section from each treatment group. 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 USA RCT compared nifedipine in combination with bed-rest with bed rest alone.¹³⁰ [EL=1+] Women were included if they had mild pre-eclampsia at 26-36 weeks 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 protein per 24 hours or at least 2+ proteinuria on dipsticks and/or elevated uric acid levels (≥ 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. 100 women received bed rest in combination with 40mg nifedipine a day, which was increased every 2 to 3 days as needed to a maximum of 120 mg/day to keep systolic pressure below 140 mmHg and diastolic 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, anti-platelet agents, rest or bed rest. A small trial of low quality¹²⁸ [EL=1-] found methyldopa effective in preventing severe pre-eclampsia compared to placebo. Another small trial¹²⁹ of low quality [EL=1-] compared methyldopa with isradipine but did not achieve any statistically significant results. One RCT¹²⁷ [EL=1+] found labetalol reduced progression to severe hypertension compared with no treatment. A well conducted trial¹³⁰ [EL=1+] found nifedipine combined with bed rest to not improve maternal or fetal outcomes compared to bed rest alone. This study did not show any statistically significant results.

GDG interpretation of the evidence

Treatment with anti-hypertensive agents

Limited good quality evidence is available in relation to treatment of pre-eclampsia. There is no evidence that blood pressure lowering treatment for mild or moderate pre-eclampsia improves pregnancy outcomes compared to 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 stroke 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 values above 90 mm Hg or 100 mm Hg) 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 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 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 was 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 (until blood pressure is less than 140/90 mmHg)	Yes (until blood pressure is less than 140/90 mmHg)	Yes (until blood pressure is less than 140/90 mmHg)
Treat	No	With oral labetalol† as first-line treatment to keep <ul style="list-style-type: none"> • diastolic blood pressure less than 80–100 mmHg • systolic blood pressure less than 150 mmHg 	With oral labetalol† as first-line treatment to keep <ul style="list-style-type: none"> • diastolic blood pressure less than 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

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†.

7.6 Fetal monitoring

Clinical effectiveness

The main evidence is presented in Section 8. Only computerised cardiotocography is studied specifically in severe pre-eclampsia and is presented here.

Routine versus computerised cardiotocography in severe pre-eclampsia

One RCT¹³¹ [EL=1+] 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 (GA: 28-34 weeks) who were managed expectantly. 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 (n= 29) or routine cardiotocography (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 difference in perinatal loss (4/29 versus 1/30: RR= 4.13, 95% CI 0.49 to 34.86), perinatal morbidity (13/29 versus 14/30: RR= 0.96, 95% CI 0.55 to 1.68) or admission to NICU (9/29 versus 9/30: RR= 1.03, 95% CI 0.48 to

2.23) between the two groups. There was also no difference in caesarean sections and Apgar < 7 (5min). 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 cardiotocograph 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).

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^{132;133} [EL=1++ and EL=1+] investigated whether early delivery or expectant management of severe pre-eclampsia in pregnancies ≤ 34 weeks 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 USA¹³² [EL=1++] and involved 95 women at 28-32 weeks with severe pre-eclampsia (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 110 mm Hg with proteinuria >500 mg/24 hrs) and elevated serum uric acid levels (>5 mg/dl). 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 ($170/110 \pm 10/5$ mmHg early delivery; $172/112 \pm 9/4$ mmHg expectant management, $p=NS$) were similar between the two groups. Early delivery women ($n=46$) were prepared for delivery, either by caesarean section or induction, 48 hours after glucocorticoids were administered. Expectant management women ($n=49$) 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 significantly higher number of neonates admitted to neonatal intensive care unit (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 it was also associated with reduced risk of small-for-gestational age 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 RCT¹³³ was conducted in South Africa. [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), and 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 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 the 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, RR5.54, 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 sections) 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,¹²¹ [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 fetal growth restriction

A multicentre RCT, the Growth Restriction Intervention Trial (GRIT)¹³⁴ [EL=1+] was undertaken in 13 European countries, including the UK, between 1993 and 2001. The study assessed the effect of immediate delivery compared with delayed delivery in (singleton and multiple) pregnancies 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); 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. [EL=1+]

A second study followed up the GRIT trial after 2 years.¹³⁵ [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, 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). [EL=1+]

A retrospective cohort study conducted in Canada¹³⁶ assessed morbidity and mortality rates for the woman and fetus in severe pre-eclampsia when managed expectantly. Women whose condition was too unstable and who required delivery within 24 hours, multifetal pregnancy, premature 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; 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 anti-hypertensives, and fetal assessment with ultrasonography and, when available, ultrasound artery Doppler velocimetry. Daily non-stress testing was done and biophysical profile 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 fetal growth restriction (< 10 th percentile) was 58.6% (91/155 pregnancies). Mean gestational age at delivery was 30.9 ± 2.1 weeks. When comparing maternal adverse outcomes between mothers whose babies were small for gestational age and those who were appropriately grown, no statistically significant differences were found with respect to renal insufficiency, pulmonary oedema, eclampsia, and 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 and sepsis). It was also found that the incidence of respiratory distress syndrome and other morbidities (IVH, NEC, BPD, sepsis and Apgar < 7 at 5-min) markedly decreased after 30 weeks. When stratified for both gestational age and fetal growth restriction \leq or $>$ 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. [EL=2+]

A retrospective population study undertaken in the Trent region of the UK¹³⁷ between 1994 and 1997 involved European and Asian live births, stillbirths and late fetal losses (excluding congenital malformations) from 22 to 32 weeks; 3760 babies were included. 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. [EL=2+]

A prospective cohort study from the USA¹³⁸ [EL=2++] looked at mortality and morbidity rates at a corrected age of 18-22 months in 4446 babies born at 22-25 weeks. 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
Week 22	95%	98%	99%
Week 23	74%	84%	91%
Week 24	44%	57%	72%
Week 25	25%	38%	54%

HELLP syndrome

A retrospective cohort study conducted in the Netherlands¹³⁹ compared fetal and maternal outcome of pre-eclampsia, with and without HELLP syndrome, to determine if expectant management increased the risk of perinatal mortality in women with HELLP. 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 (≤ 12 days' difference). There was no statistically significant difference in the mean diastolic blood pressure between the two groups. Systolic blood pressure, however, was 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 h), antihypertensive treatment (if diastolic BP 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 (0-59) in the HELLP group, and 9 days (0-63) in the group without HELLP. No cases of maternal mortality, pulmonary oedema or renal insufficiency were reported. 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, major handicaps). Multivariate regression analysis using diagnosis of HELLP 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). [EL=2+]

Cost effectiveness

The literature search did not identify any published economic evaluations comparing immediate birth with expectant management in women with mild or moderate pre-eclampsia pre-term (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 with mild or moderate pre-eclampsia at 34-37 weeks. However for this health economic model we used data from a retrospective case-control study undertaken in the USA.¹⁴⁰ 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 to expectant management in women with mild or moderate pre-eclampsia pre-term 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 an ongoing 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 <http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=1792>).

Evidence statement

Pooled results from two good quality RCTs [EL=1++, 1+] indicate that babies whose mothers underwent early delivery had increased risk of hyaline membrane disease and necrotising enterocolitis and were more likely to need admission to neonatal intensive care units than those whose mother received expectant management. Nevertheless, babies in the early delivery group were less likely to be small-for-gestational age. 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 or 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 and 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 was that the lack of evidence of benefit in prolonging pregnancy beyond 34 weeks in women with severe pre-eclampsia justified offering birth after 34 weeks. The economic analysis also showed that offering birth after 34 weeks was cost effective. The analysis also showed that the incidence of severe disease was the main determinant of cost effectiveness.

Although fetal growth restriction 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 small-for gestational-age 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 of mild and moderate pre-eclampsia at or before 36 weeks, although one RCT provided clear evidence of the clinical and cost effectiveness of immediate birth after 36 weeks.¹²¹ [EL 1+]

The GDG feel that as a proportion of women with mild or moderate pre-eclampsia 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 trial¹²¹ [EL 1+] confirmed that there is no maternal or immediate neonatal disadvantage with immediate birth after 37⁺⁰ weeks in women with mild or moderate pre-eclampsia. 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, and so the GDG recommends birth within 24–48 hours for women with mild or moderate pre-eclampsia 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 was that a consultant or specialist review of the individual case was 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 (clinical, biochemical and haematological) and fetal thresholds for elective birth before 34 weeks in women with pre-eclampsia.

Consultant obstetric staff should write a plan for 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 antenatal steroids 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 with severe pre-eclampsia after 34 weeks when their blood pressure has been controlled and a course of antenatal steroids has been completed (if appropriate).

Offer birth to women with mild or moderate pre-eclampsia 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 with mild or moderate pre-eclampsia after 37⁺⁰ weeks.

Research recommendations

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

Why this is important

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

Women with mild or moderate pre-eclampsia 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 with mild or moderate pre-eclampsia 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 different 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 1,979 references, of which 31 were retrieved. There was no evidence for observations or monitoring.

Antihypertensives

Six RCTs were identified, two of which had evidence level of [EL=1+] ^{141,142} and four had evidence level of [EL=1-] ^{122,143-145}.

Need for anti-hypertensive agents postnatally

A small RCT from the USA [EL 1-] ¹⁴³ investigated the efficacy of nifedipine in controlling hypertension and improving urine output in postpartum women with severe pre-eclampsia. Women were randomly allocated (using a random number table) to either receive nifedipine (n=16) (10 mg orally every 4 hrs for 48 hours) immediately after delivery or placebo (n=15). The process of concealment allocation was adequate. Baseline characteristics of women from both groups were comparable.

There were no cases in either group which needed additional antihypertensive therapy. There was also no change in treatment due to maternal side-effects in either groups or any reported cases of significant hypotension.

Comparison of antihypertensive agents

Hydralazine versus labetalol

A RCT [EL=1+] ¹⁴¹ was conducted in Panama compared two antihypertensive agents postnatally in women with severe hypertensive disorders. Eighty-two women were randomly allocated using a computer generated list by means of sequentially numbered opaque sealed envelopes to either receive intravenous hydralazine (n=42) (5mg bolus repeated every 20 min) or intravenous labetalol (n=40) (20 mg bolus followed by 40 mg increased up to 300 mg). Baseline characteristics for women from both groups were comparable.

No 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 between the two groups. There was also no difference in those who developed HELLP syndrome or oliguria.

Timolol versus methyldopa

A RCT from the UK [EL=1-] ¹²² compared the use of timolol and methyldopa in the management of puerperal hypertension. Untreated postpartum women with diastolic blood pressure (95-105 mmHg) were randomly allocated to either receive timolol (n=40) (5mg orally, 3 times a day) or methyldopa (n=40) (250 mg orally, 3 times a day). In both cases, the dose was doubled every 24 hours twice if diastolic blood pressure was > 95 mmHg. Antenatally, 46 of the 80 women had received drug treatment for hypertension and another 14 had had mild hypertension (<95 mmHg) which did not require treatment. The remaining 20 women were not 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 significant difference in the number of those who had their medications changed due to maternal side-effects (1/40 versus 2/40: RR=0.50, 95% CI 0.05 to 5.30).

Hydralazine versus methyldopa

An RCT from the USA [EL=1-] ¹⁴⁵ 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. 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 (n=12) (20 mg every 6 hours) or intravenous methyldopa (n=14) (250 mg every 6 hours).

There were no differences in the need to augment the dose between the two groups. There were no cases in either of the two groups needing additional antihypertensive therapy or change in treatment due to maternal side-effects.

Diuretics

An RCT from the USA [EL=1+] ¹⁴² investigated whether a brief postpartum course of furosemide for women with pre-eclampsia benefited recovery and shortened hospitalisation. Two hundred sixty-four women with hypertension during their pregnancies were enrolled in the study (169 women of those had mild pre-eclampsia, 70 had severe pre-eclampsia or HELLP syndrome while 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 (20mg daily together with an oral potassium supplement 20mEq 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 significantly less likely to need additional antihypertensive medication during hospitalisation in comparison with those who received no medication (46/132 versus 62/132: RR=0.74, 95% CI 0.55 to 0.997). As for the use of additional antihypertensive medication at time of hospital discharge, there was no statistically significant difference between the two groups (38/132 versus 49/132: RR=0.78, 95% CI 0.55 to 1.10). However, when results were stratified by type of hypertensive disorder, the only outcome which became significant was the need for additional antihypertensive in women with severe pre-eclampsia/HELLP syndrome (2/35 versus 9/35: RR=0.22, 95% CI 0.05 to 0.96).

A small RCT from the UK [EL=1-] ¹⁴⁴ investigated diuretics use postnatally to lower blood pressure in women with severe pre-eclampsia and consequently shorten their hospital stay and need for professional supervision. Nineteen women with severe pre-eclampsia were randomly allocated to receive either furosemide (n=10) (40 mg/day orally) or placebo (n=8) in a double blind trial.

There was no significant difference in the need for antihypertensive medication between the two groups (3/10 versus 3/8: RR=0.8, 95% CI 0.22 to 2.93). Oliguria at discharge did not differ between the two groups (3/10 versus 2/8: RR=1.2, 95% CI 0.26 to 5.54).

Evidence statement

Three trials have compared the effectiveness of different antihypertensive drugs (hydralazine versus labetalol, timolol versus methyldopa, hydralazine versus methyldopa). Results from these trials (one with EL 1+ and 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 apply to 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 the non-pregnant woman. Abnormal results at 6 weeks may indicate an abnormality which requires further investigation.

Both persistent significant proteinuria (2+ on dipstick) and blood pressure which 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 34.²⁹

Recommendations

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 have given birth, aim to keep blood pressure lower than 140/90 mmHg.

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:

- 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.

In women with pre-eclampsia who have taken antihypertensive treatment and have given birth, continue antenatal antihypertensive treatment.

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.

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 with mild or moderate pre-eclampsia 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 urine dipstick 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 different 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 10 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 fetal growth restriction, 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^{146;147} [EL=1+] were identified which reported data on the use of umbilical Doppler for fetal assessment in women with hypertensive disorders in pregnancy.

One RCT from South Africa¹⁴⁷ [EL=1+] assessed whether the results of Doppler umbilical artery velocimetry were beneficial to the management of a high risk pregnancy. Recruited women were divided into three groups based on the outcomes of Doppler examinations: Group-1 (n=20) those with fetuses with absent end-diastolic velocities, Group-2 (n=89) those with hypertension but with fetuses with end-diastolic velocities and Group-3 (n=104) those with fetuses suspected of being small for gestational age but with end-diastolic velocities.

For the hypertensive subgroup (Group-2), women were randomised into either study group (n=47) in which Doppler velocimetry was revealed to clinicians or control group (n=42) in which Doppler velocimetry was withheld from clinicians.

Randomisation was achieved using a balanced block technique and allocation was inserted into an opaque sealed envelope.

There was no significant difference in the two groups in terms of perinatal deaths (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 was also no difference in gestation at delivery, birthweight, hospitalisation for either the woman or the infant, spontaneous labour, or caesarean sections.

One RCT from Canada¹⁴⁶ [EL=1+] compared the use of umbilical artery Doppler with non-stress test in women with high risk pregnancy (N=1,340). Participants were \geq 32 weeks who had hypertensive disorders, diabetes that required insulin, suspected IUGR, postdates or patient-perceived decrease in fetal movement for > 24 hours. Exclusion criteria included women with premature rupture of membranes, multiple pregnancies, fetal death in uterus, known lethal fetal anomaly, known fetal cardiovascular anomaly, 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 random number table. Women were either allocated to the Doppler group (n=691) or electronic fetal heart rate (FHR) using the non-stress test (NST) (n=691). Doppler 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 delivery for fetal distress. Women who had hypertensive disorders (N=148, 67 in the Doppler group, 81 in the NST group), were significantly less likely to have a caesarean section for fetal distress if they were in the Doppler group than in the NST group (1/67 versus 11/81: RR=0.11, 95% CI 0.02 to 0.83).

Evidence statement

Evidence from two relatively small RCTs [EL=1+] showed no significant improvement in neonatal outcomes including death and admission to NICU in infants of women with hypertensive disorders monitored by umbilical Doppler. However, women were less likely to require a caesarean section for fetal distress if Doppler was used.

Women with high-risk pregnancies

We identified one systematic review¹⁴⁸ [EL=1++] and an additional later RCT¹⁴⁶ [EL=1+].

The systematic review¹⁴⁸ [EL=1++] included 13 RCTs published between 1987 and 1994 (Overall number of participants= 8633) which looked at the use of umbilical artery Doppler ultrasound in high-risk pregnancies (published and unpublished reports) in comparison with no-Doppler or routine monitoring. They divided the RCTs into 'well-defined' studies (6 of 13 studies, N=2159). Those included only singleton pregnancies with suspected IUGR (n= 1307) and/or hypertensive disease of pregnancy (n=852). The 'general risk' studies (7 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% had other high risk complications.

12 of the included studies used adequate randomisation and concealment methods while two used a quasi-randomised approach. Interpretation of waveform indices: 3 RCTs of the well defined studies used pulsatility index (PI),

2RCTs used resistance index (RI), and one used systolic/diastolic ratio. Four of the general risk studies used RI, one used PI and 3 RCTs used systolic/diastolic ratio.

Perinatal mortality of non-malformed singletons was 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-min (OR=0.89, 95% CI 0.74 to 0.97). Women monitored with umbilical Doppler were less likely to be admitted antenatally (OR=0.56, 95% CI 0.43 to 0.72) and to require emergency caesarean sections (OR= 0.85, 95% CI 0.74 to 0.97).

When considering all high risk studies, there was no significant difference between the two groups in terms of induction of labour, elective delivery, admission to NICU or caesarean sections. However, subgroup analysis of well-defined studies showed women monitored with umbilical Doppler to be significantly less likely to be induced (OR=0.78, 95% CI 0.63 to 0.96), 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 the Canada¹⁴⁶ [EL=1+] (described above*) investigated the use of umbilical Doppler for screening high-risk pregnancies. It showed women with high-risk pregnancy to be more likely to be induced for abnormal testing (31/649 versus 13/691: RR= 2.53, 95% CI 1.34 to 4.81) but less likely to have caesarean section delivery for fetal distress (30/649 versus 60/691: RR=0.53, 95% CI 0.35 to 0.81). However, there were no significant differences in terms of 1-min Apgar score < 4, 5-min Apgar score ≤ 7, vaginal operative delivery, and caesarean section delivery excluding fetal distress as an indication, admission to NICU, and birthweight. There was only one stillbirth case and it was in the no-Doppler group.

Evidence statement

One systematic review [EL=1++] showed that use of Doppler for fetal assessment in women with high-risk pregnancies reduced perinatal mortality and babies born with low Apgar score at 5-min. Women monitored with umbilical Doppler were less likely to be admitted antenatally and to require emergency caesarean sections. Subgroup analysis of well-defined studies showed women monitored with umbilical Doppler to be significantly less likely to be induced, have elective delivery, or caesarean section.

One additional RCT [EL=1+] showed women with high risk pregnancy monitored with Doppler to be more likely to be induced for abnormal testing, but less likely to have caesarean section delivery for fetal distress.

GDG interpretation of the evidence

Whilst one study which 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 review¹⁴⁹ [EL=1+] looked at RCTS which investigated the use of cardiotocography (CTG) against alternative methods of assessing fetal health (CTG and withholding the result from the caregiver or a non-monitored group). Participants were women at low and high risk obstetric risk including women with hypertensive disorders which composed different percentages of the main sample of all included trials.

In three trials, CTGs were 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 being 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 CTG group (3 RCTs, n=1279: Peto OR=2.65, 95% CI 0.99 to 7.12). Besides, there was an increase number of admitting outpatients and keeping inpatients in hospital in CTG group (one RCT, n=300: Peto OR=0.37, 95% CI 0.17 to 0.83) and (one RCT, n=300: Peto OR=0.43, 95% CI 0.21 to 0.89), respectively. No differences were found in onset of labour (spontaneous, elective CS or labour induction), methods of delivery (normal vaginal birth, operative vaginal birth or caesarean sections). There was also no significant difference 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 CTG had no different outcomes from those who were not monitored. Instead, there tends to be higher perinatal mortality risk in babies of women monitored with CTG.

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 they recommend 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 RCT¹³¹ [EL=1+] from South Africa compared the use of computerised CTG with routine CTG in monitoring fetal heart rate of women with severe early onset pre-eclampsia (GA: 28-34 weeks) who were managed expectantly. 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 CTG (n= 29) or routine CTG (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 FHR monitoring was done with a computerised monitor and visually assessed.

The study showed no difference in perinatal loss (4/29 versus 1/30: RR= 4.13, 95% CI 0.49 to 34.86), perinatal morbidity (13/29 versus 14/30: RR= 0.96, 95% CI 0.55 to 1.68) or admission to NICU (9/29 versus 9/30: RR= 1.03, 95% CI 0.48 to 2.23) between the two groups. There was also no difference in caesarean sections and Apgar < 7 (5min). 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 cardiotocogram 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 computerized CTG in hypertensive pregnancies

8.6 Biophysical profile

Clinical effectiveness

One Cochrane systematic review¹⁵⁰ [EL=1+] assessed the effect of the BPP when compared with conventional monitoring (CTG only or modified BPP). Participants were at > 24 weeks with singleton, high-risk pregnancies. The review included five trials. In one RCT (N=145) women had post-term pregnancy, in another one (N=135) women had rupture of membrane. In the rest 3RCTs included, women had variety of high-risk pregnancies of which hypertension composed 12%, 12% and 27% respectively of the sample studied. Modified biophysical profile composed of CTG 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 2 RCTs.

Four studies (n=2829) compared BPP with CTG. One trial (n=145) compared complete BPP with CTG and amniotic fluid assessment using SDP technique. Pregnancies were managed on the basis of normal or abnormal test results. Although not all trials reported the GA 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 4 RCTs, N=2829), whereas the mean GA in one RCT (n=135) was 24.2 weeks.

Babies born to women monitored with BPP stayed for shorter periods in NICU (2RCTs, N=1442, Standard MD=0.20, 95% CI 0.09 to 0.30). However, data on length of stay were skewed due to gross pre-maturity in one RCT (N=135) and are therefore unreliable. Women in the BPP group were more likely to be induced in general (1RCT, N=145, RR=1.45, 95% CI 1.04 to 2.03) and induced for abnormal fetal assessment in specific (1 RCT, N=135, RR=2.58, 95% CI 1.39 to 4.78).

There was no difference in perinatal deaths or admission to NICU between the two groups. Similarly, no difference was found in Apgar score < 7 at or after 5 min, small-for-gestational age, meconium, respiratory distress syndrome, caesarean section for fetal distress. However, subgroup analysis of the high

quality trials showed a significantly higher level of caesarean sections in the BPP group (2RCTs, N=280, RR=1.60, 95% CI 1.05 to 2.4).

Evidence statement

A Cochrane systematic review¹⁵⁰ [EL=1+] which investigated the use of biophysical profile in women with high-risk pregnancy found no significant difference between those monitored by BPP and those monitored by CTG or modified BPP in terms of perinatal death or admission to NICU. It also showed no difference in Apgar score < 7 at or after 5 minutes, small-for-gestational age or caesarean section. Women monitored with BPP were 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

One Cochrane systematic review¹⁵¹ [EL=1++] 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.

The review looked at RCTs involving women with a singleton pregnancy, whether at low or high risk, undergoing tests for assessment of fetal well-being.

Four RCTs (N=3125) were included. All four trials were of high quality. All included trial reports which 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 (102/537, 88/1000 and 127/1088). 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, perinatal death).

When the amniotic fluid index was used, significantly more cases of oligohydramnios were diagnosed (4RCTs, N=3125, RR=2.33, 95% CI 1.67 to 3.24) and more women had inductions of labour (3RCTs, N=2037, RR=2.10, 95% CI 1.60 to 2.76) and caesarean deliveries for fetal distress (4RCTs, n=3125: RR=1.45, 95% CI 1.07 to 1.97).

No significant differences were found in other secondary outcomes like Umbilical artery pH < 7.1, Apgar score < 7 at 5-min, presence of meconium, non-reassuring fetal heart rate tracing, assisted vaginal delivery, assisted vaginal delivery for fetal distress and caesarean delivery.

Evidence statement

A Cochrane review [EL=1++] showed that in women at 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 of less than 7.1, the presence of meconium, an Apgar score of less than 7 at 5-min or caesarean delivery. When the amniotic fluid index was used, significantly more cases of oligohydramnios were diagnosed and more women had induction of labour and caesarean deliveries 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 pool – 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,¹⁵² [EL=1+] involving women receiving maternity care from an obstetrician, a clinic (no further details reported), or a hospital during treatment investigated whether routine formal counting, backed by appropriate action resulted in a clinically important improvement in neonatal outcomes. The study recruited 68,654 women (28-32 weeks) and divided them into 66 clusters (about 1,000 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 for risk of antepartum late fetal death and randomly allocated to the experimental (or control policy within the matched pairs (33 clusters= 31,993, fetal movement count; 33 clusters= 36,661 no instruction).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, 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 significant difference was found between the two groups in terms preventing stillbirth (N=33 each: 2.9 ± 1.9 versus 2.67 ± 1.55 : MD 0.23, 95% CI from - 0.61 to 1.07). Women in the experiment group were not different from those in the control group in terms of antenatal admission or undergoing CTGs or being induced or having elective caesarean section. Women in the routinely counting group were more prone to feeling anxious in late pregnancy (MD 2.0 per 100 women, 95% CI 1.8 to 5).

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 or undergoing labour induction or elective caesarean. Women in the routine counting group were, however, more prone to feeling anxious in late pregnancy.

GDG interpretation of the evidence

Evidence shows 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 62.²⁴ However women with hypertensive disorders of pregnancy should be encouraged to be aware of their baby's movements and report perceived changes to their healthcare professionals.

8.9 Uterine artery Doppler velocimetry in high-risk pregnancies

Clinical effectiveness

Seven diagnostic studies^{73-77;153;154} [EL=II] investigated the use of uterine artery Doppler 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), albumin creatinine ratio (A:C).

Results are presented below by population stratified according to risk factors: previous pre-eclampsia; chronic hypertension (see Section 3.5.1); kidney disease; and mixed risks. An HTA report³⁷ and a systematic review and meta-analysis published by the same research team¹⁵⁵ 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.

8.9.1 Women with previous pre-eclampsia

One prospective diagnostic study¹⁵³ [EL=II] studied women with previous pre-eclampsia (n=56; see Table 8.1). Two of these women had eclampsia and 24 cases had early-onset pre-eclampsia (<34 weeks), 17 had also IUGR and 6 had also intrauterine fetal demise. All women underwent uterine Doppler test at 24 weeks. Low dose aspirin was given to women from 12 weeks gestation.

Endpoint, pre-eclampsia: using resistance index (RI) to interpret Doppler results (abnormal: > 0.58) showed a sensitivity of 100% and specificity of 60%. Unilateral or bilateral notches showed a sensitivity of 100% and specificity of 66% while using both bilateral notches showed a sensitivity of 33% and specificity of 87%.

Endpoint, SGA: using resistance index (RI) to interpret Doppler results (abnormal: > 0.58) showed a sensitivity of 85% and specificity of 70%. Unilateral or bilateral notches showed a sensitivity of 85% and specificity of 77% while using both bilateral notches showed a sensitivity of 46% and specificity of 95%.

Women with kidney disease

One prospective diagnostic study¹⁵⁴ [EL=II] used uterine Doppler (19-24 weeks gestation) in pregnant women with known kidney disease (other than diabetic nephropathy; see Table 8.1). Renal function was considered decreased if two out of following three are abnormal – plasma creatinine (≥ 90 micromol/l), plasma urea (≥ 6.5 mmol/l), creatinine clearance (≤ 1.5 ml/sec).

51 women were included; 24 of which had primary glomerulonephritis, 19 had reflux nephropathy, 5 had glomerulonephritis secondary to a systemic disease and 3 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 women were untreated during the whole pregnancy.

Endpoint, pre-eclampsia: using resistance index (RI) to interpret Doppler results (abnormal: > 90th percentile of reference group) showed a sensitivity of 50% and specificity of 75%. A/C ratio showed a sensitivity of 50% and specificity of 79%.

Endpoint, IUGR: using resistance index (RI) to interpret Doppler results (abnormal: > 90th percentile of reference group) showed a sensitivity of 83% and specificity of 80%. A/C ratio showed a sensitivity of 83% and specificity of 84%.

Table 8.1 Use of uterine Doppler to predict pre-eclampsia/growth restriction in women with previous pre-eclampsia or kidney disease

	Study	Population Demographic characteristics	GA	Index		PE	IUGR	Notes
Previous PET	Frusca 1996 Country: Italy ¹⁵³	N=56 previous PET 2 cases had eclampsia, 24 cases had an early onset PE (<34 wks gestation), 17 had also IUGR and 6 had also intrauterine fetal demise.	24 wks	RI: Abnormal=>0.58	Sens: 100% Spec: 60% PPV: 13% NPV: 100%	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 PET. PE= dBP> 90mmHg, proteinuria >0.3 g/24h Endpoint: PE
Renal disease	Ferrier 1994 Country: New Zealand ¹⁵⁴	N= 51 with kidney disease (other than diabetic nephropathy)	19-24 wks	RI: abnormal > 90 th percentile	Sens: 50% Spec: 75% PPV: 14% NPV: 95%	50% 75% 14% 95%	83% 80% 36% 97%	Renal function decreased if 2 out of the 3 was abnormal: Plasma creatinine (≥ 0.09 mmol/l), plasma urea (≥ 6.5 mmol/l), creatinine clearance (≤ 1.5 ml/sec). Reference: control group of 458 low-risk nulliparous women studied same period Endpoints: PE

Women with mixed high risk factors

Three diagnostic studies⁷⁵⁻⁷⁷ [EL=II] investigated the use of uterine Doppler at 22-24 weeks gestation in women with high risk pregnancy (previous pre-eclampsia, previous stillbirth, previous abruptio placentae, previous IUGR, chronic hypertension, diabetes, autoimmune disease, kidney disease, habitual abortion). Descriptions of included studies are in table 2. Using resistance index gave a sensitivity of 78-97% and specificity of 42-71% on prediction of pre-eclampsia. One of these studies⁷⁷ (n=116) reported data on the use of RI in predicting IUGR. It gave a sensitivity of 84% and specificity of 39%.

Table 8.2 Use of uterine Doppler to predict pre-eclampsia/growth restriction in women with high risk pregnancies

	Study	Population Demographic characteristics	GA	Index	Parameters	PE	IUGR	Notes
Mixed high risk	Parretti 2003 Country: Italy ⁷⁵	N=144, previous PET (n=87), previous stillbirth (n=22), previous abruptio placentae (n=11), previous fetal growth restriction (n=24) Age: 34.5 (27-41), gravidity 2(2-3), parity: 1(1-2)	24 wks	RI: abnormal ≥ 0.58	Sens: Spec: PPV: NPV:	77.8% 67.6% 44.4% 90.1%	Not reported	Exclusion: smoking, kidney disease, CVD, DM, multiple pregnancy, fetal chromosomal abnormalities, or if already on low-dose aspirin PE=BP>140/90mmHg, proteinuria>0.3 g/24h. Endpoint: PE
	Caforio 1999 Country: Italy ⁷⁶	N= 335, CH (n=89), PE (n=76), IDDM (n=58), autoimmune disease (n=53), SLE (n=17), kidneydisease (n=34), previous stillbirths (n=91), IUGR (n=20) and habitual abortion (n=119) Age 31 \pm 4.8 yrs	N=249 at 22-24 wks	RI: abnormal > 90th percentile	Sens: Spec: PPV: NPV:	97% 71% 31% 99%.	77% 72% 37% 94% (Endpoint: birthweight <1,750 gm)	Exclusion: congenital defects, chromosomal abnormalities, multiple gestations, infections, Rh isoimmunisation, nonimmune hydrops, premature rupture of the membranes, intrauterine deaths or delivery prior to 26 weeks gestation. (reference ranges previously obtained in our laboratory from 1,084 healthy pregnancy) Endpoint: PE
	Coleman 2000 Country: New Zealand ⁷⁷	N=116, CH (n=69), previous recurrent PE (n=24), previously early-onset PE requiring delivery at \leq 32 weeks (n=25), previous placental abruption (n=10), kidneydisease (n=40), SLE (n=13), antiphospholipid syndrome (n=5) Age: 31 (19-43) yrs. 31/116 were nulliparous and 18% smoked during pregnancy.	22-24 wks	RI: any abnormal >0.58	Sens: Spec: PPV: NPV:	91% 42% 37% 92%	84% 39% 33% 87%	Exclusion: multiple pregnancies and pregnancies with recognised fetal abnormalities. Endpoint: PE * Data for Both RI >0.58, any notch, and Any RI and any notch are also reported.
				Bilateral notch	Sens: Spec: PPV: NPV:	29% 86% 47% 74%	36% 89% 53% 79%	

Evidence statement**Prediction of pre-eclampsia**

Women with previous pre-eclampsia: one diagnostic study [EL II] showed that uterine Doppler at 24 weeks gestation has a sensitivity of 100% and specificity of 60% to predict pre-eclampsia when using resistance index; and a sensitivity of 100% and specificity of 66% when using unilateral or bilateral notches.

Women with kidneydisease: one diagnostic study [EL II] showed that uterine Doppler at 19-24 weeks gestation has sensitivity of 50% and specificity of 75% when using resistance index and sensitivity of 50% and specificity of 79% when using A/C ratio.

Women with mixed high risk factors: Three diagnostic studies [EL II] showed that uterine Doppler at 22-24 weeks gestation has sensitivity of 78-97% and specificity of 42-71%.

Prediction of intrauterine growth restriction

Women with previous pre-eclampsia: one diagnostic study [EL II] showed that uterine Doppler at 24 weeks gestation has a sensitivity of 85% and specificity of 70% to predict IUGR when using resistance index; and a sensitivity of 77% and specificity of 46% when using unilateral or bilateral notches.

Women with kidney disease: one diagnostic study [EL II] showed that uterine Doppler at 19-24 weeks gestation has sensitivity of 83% and specificity of 80% when using resistance index and sensitivity of 83% and specificity of 84% when using A/C ratio.

Women with mixed high risk factors: one diagnostic studies [EL II] showed that uterine Doppler at 22-24 weeks gestation has sensitivity of 84% and 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.

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 Section 10) and of fetal growth restriction. The GDG feels that limited routine surveillance of fetal growth is justified for these women.

Recommendations

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 antenatal steroids 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.

Research recommendations

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. 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 section 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 Section 8.

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 feel 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

Evidence: see Section 10 for severe disease and Sections 6 and 7 for tests and frequency in 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).

Recommendations

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

We included three RCTs¹⁵⁶⁻¹⁵⁸. All RCTs compared epidural with intravenous analgesia. Populations, however, were different for each trial; hypertensive disorders during pregnancy¹⁵⁸ [EL=1+], pre-eclampsia¹⁵⁷ [EL=1-] and severe pre-eclampsia¹⁵⁶ [EL=1+] (see table 9.1).

Women with hypertensive disorders in pregnancy

A RCT¹⁵⁸ [EL 1+] from the USA compared the peripartum and perinatal effects of epidural with intravenous labour analgesia in 738 women with pregnancy-induced hypertension (dBp \geq 90 mmHg) who were admitted to labour (exclusion criteria: table 9.1).

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, 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 (242/372 versus 273/366, p=0.005).

Women receiving epidural analgesia had significantly longer 2nd stage labour than those receiving intravenous analgesia (2nd stage: 53 \pm 50 versus 40 \pm 42 min, p=0.002). They were also more likely to develop intrapartum fever (76/372 versus 26/366: RR=2.88, 95% CI 1.89 to 4.38). The mean arterial pressure decrease after analgesia was higher in the epidural group (25 \pm 18 versus 13 \pm 14, p<0.001) and they were more likely to be given ephedrine to treat this hypotension (40/372 versus 0/366: RR=79.70, 95% CI 4.92 to 1291.32) and to receive intrapartum intravenous fluids (1525 \pm 859 versus 954 \pm 747 ml: p<0.001).

Instrumental vaginal births (forceps) were significantly higher in the epidural analgesia group (51/372 versus 27/366: RR=1.86, 95% CI 1.19 to 2.90). No differences in spontaneous vaginal birth or caesarean sections were found between the two groups. Need for oxytocin induction was higher in the intravenous group (100/372 versus 181/366: RR= 0.54 (0.45 to 0.66). However, no

difference was found in the need for oxytocin augmentation (152/372 versus 129/366: RR=1.16 (0.96 to 1.40)

The neonatal outcomes of 5-min Apgar scores (≤ 3 and < 7), admission to NICU and need for ventilation in the first 24 hrs were similar in the groups. The number of babies with umbilical artery pH < 7.0 or < 7.1 was also similar in the groups. However, babies of women treated with intravenous analgesia were more likely to have umbilical artery pH < 7.2 (21/372 versus 41/366: RR=0.50 (0.30 to 0.84). They were also more likely to be given naloxone (2/372 versus 40/366: RR= 0.05 (0.01 to 0.20).

Women with pre-eclampsia

One RCT¹⁵⁶ [EL 1-] from India assessed the use of labour epidural analgesia in 200 nulliparous women with pre-eclampsia (exclusion criteria: table 9.1). Participants were randomly allocated by 'rule of odds to even' into epidural analgesia group (n=100) and '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, body mass index, and gestational period.

The study showed no difference in mode of delivery (normal vaginal, instrumental vaginal and caesarean section) between the two groups. Indications for instrumental deliveries (fetal distress, prophylactic, non-progressive 2nd stage) and indications for caesarean sections (fetal distress, cephalopelvic disproportion, non-progressive 1st stage) were the same between the two groups. The incidence of a prolonged 2nd stage of labour was not different between the groups (3/100 versus 1/100: RR=3.00, 95% CI 0.32 to 28.36).

Neonatal outcomes were similar between the groups including 5-min Apgar score < 6 (5/100 versus 7/100: RR=0.71, 95% CI 0.24 to 2.18) and the necessity of neonatal resuscitation (14/100 versus 13/100: RR=1.07, 95% CI 0.53 to 2.1).

Women with severe pre-eclampsia

An RCT¹⁵⁷ [EL 1+] from the USA investigated the relationship between intrapartum analgesia and the caesarean delivery rate in women with severe pre-eclampsia. 116 women with severe pre-eclampsia who were in labour with a singleton pregnancy and vertex presentation were randomly allocated to epidural analgesia group (n=56) or 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 (excluded criteria: table 9.1). Baseline maternal demographics (age, weight, nulliparous, race, gestational age and initial cervical dilation) were comparable between the two groups.

The study showed no differences in mode of delivery or indications for caesarean section between the two groups. Incidence of seizure, mechanical ventilation and oliguria were also similar. However, the mean intrapartum pain scores were significantly lower (4 ± 3 versus 7 ± 3 , $p < 0.001$) and the median postpartum satisfaction scores significantly higher in the epidural group (median 3 (1-4) versus median 2(1-4), $p = 0.002$). There was also a trend towards a higher use of ephedrine in the epidural group but this did not reach statistically significant level (5/56 versus 0/60: RR=11.77, 95% CI 0.67 to 208.14).

Babies from the opioid group received naloxone more often at the time of delivery (5/56 versus 31/60: RR=0.17, 95% CI 0.07 to 0.41). Other neonatal outcomes were similar between the groups including neonatal death (3/56 versus 0/60: RR= 7.49 (0.40 to 141.87)) and admission to NICU (45/56 versus 44/60: RR=1.06 (0.87 to 1.29)). Similarly, the number of neonates with Apgar score < 7 at 1-min and at 5-min was not different between the two groups.

Table 9.1 Use of epidural analgesia in women with hypertensive disorders during pregnancy

Study	EL	N	Population	Exclusion	Intervention: Epidural analgesia	Comparison:
Lucas et al (2001) ¹⁵⁸ Country : USA	1+	738 (372, 366)	Pregnancy induced hypertension (dBP ≥ 90 mmHg)	-Treated chronic hypertension -Prior analgesia/sedation -Contraindication to labour and/or vaginal delivery	I.v.i 500 ml of lactated Ringer's solution; then bolus (epidural injection) of 0.25% bupivacaine followed by a continuous epidural infusion (0.125% bupivacaine with 2 mg/ml of fentanyl). [T10 sensory level]	Intravenous analgesia: I.v bolus 50mg meperidine with 25mg promethazine. Infusion pump was then used (max 15 mg meperidine every 10min) if needed.
Patel et al (2005) ¹⁵⁶ Country : 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)	I.v.i 540ml of lactated Ringer's solution; then bolus (epidural injection) of 8ml bupivacaine HCl 0.125% with tramadol 50 mg. [T10 to L1 sensory level]	No epidural analgesia: I.M tramadol 50 mg for pain relief.
Head et al (2002) ¹⁵⁷ Country : USA	1+	116 (56, 60)	Severe pre-eclampsia (singleton; vertex; >24 wks; dilation <5 cm)	-Platelet count < 80x10 ⁹ /L -Pulmonary oedema -Non-reassuring FHR requiring imminent delivery -Abnormal airway examination that might predict an increased risk of difficult intubation.	I.v.i 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 mcg/ml at an initial rate of 10 ml/h). [T10 sensory level]	Intravenous analgesia: i.v meperidine hydrochloride via patient-controlled analgesia device. The self-administered dose was 10 mg, with a lock-out interval of 10 minutes (max dose: 240 mg every 4-hr)

Evidence statement

Gestational hypertension

An RCT [EL 1+] which compared epidural and intravenous analgesia at labour in women with pregnancy-induced hypertension showed that women receiving epidural analgesia had significantly longer 2nd stage labour (53 ±50 versus 40 ±42 min, $p=0.002$) and were more likely to develop intrapartum fever (76/372 versus 26/366: 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 versus 13 ±14, $p<0.001$). Women given epidural analgesia were more likely to be given ephedrine to treat hypotension (40/372 versus 0/366: RR=79.70, 95% CI 4.92 to 1291.32) and to receive intrapartum i.v fluids (1525± 859 versus 954 ±747 ml: $p<0.001$).

Instrumental vaginal births (forceps) and need for oxytocin induction were significantly higher in the epidural analgesia group (51/372 versus 27/366: RR=1.86, 95% CI 1.19 to 2.90) and (100/372 versus 181/366: RR= 0.54 (0.45 to 0.66), respectively.

Babies of women treated with intravenous analgesia were more likely to have umbilical artery pH <7.2 (21/372 versus 41/366: RR=0.50 (0.30 to 0.84) and to require naloxone (2/372 versus 40/366: RR= 0.05 (0.01 to 0.20). No differences were found in other neonatal outcomes.

Pre-eclampsia

One RCT [EL 1-] compared epidural analgesia with no-epidural analgesia (intramuscular tramadol). It showed no difference in mode of delivery, indications for caesarean section or instrumental vaginal birth between the two groups. The incidence of a prolonged 2nd stage of labour was not different between the groups. Neonatal outcomes were also similar between the groups.

Severe pre-eclampsia

Mean intrapartum pain scores were significantly lower ($p < 0.001$) and median postpartum satisfaction scores 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 (5/56 versus 0/60: RR=11.77, 95% CI 0.67 to 208.14). Babies from the opioid group received naloxone 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, Apgar score < 7 at 1-min and 5-min).

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 studies do not appear to demonstrate different effects of epidural analgesia in women with hypertensive disorders compared with the general obstetric population. The GDG 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.

Recommendations

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

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 stroke 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 2nd stage of labour. However, the GDG does not consider the 2nd stage of labour should routinely be shortened in women with stable mild- moderate hypertension. Consideration should be given to limiting the duration of the 2nd stage of labour in women with severe hypertension 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

Evidence: See IPC guideline

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 RCOG guidance in this area. This section reviews the evidence for the acute management of severe pre-eclampsia that is conducted within a critical care setting, 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 different interventions: antihypertensive drugs, anticonvulsant drugs, steroids for HELLP syndrome (to prolong pregnancy) and for fetal lung maturity, 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 3,379 references, of which 152 were retrieved.

10.2 Anticonvulsants

Clinical effectiveness

Six high-quality publications were identified.¹⁵⁹⁻¹⁶⁴ [EL=1++] Four of these were Cochrane systematic reviews;¹⁵⁹⁻¹⁶² the remaining two were separate publications which reported follow-up data from a single large double-blind RCT,^{163;164} which was included in one of the Cochrane systematic reviews.¹⁶² Of the Cochrane systematic reviews, one examined magnesium sulphate and other anticonvulsants for the prevention of eclampsia in women with pre-eclampsia,¹⁶² and the other three compared magnesium sulphate with other anticonvulsants for the treatment of eclampsia.^{159 160 161}

Prevention of eclampsia

Magnesium sulphate versus placebo or no treatment

A Cochrane systematic review¹⁶² [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 ≥ 2 signs or symptoms of imminent eclampsia, or BP \geq 170/110 mmHg and 3+ proteinuria or, if on antihypertensive treatment, 150/110 mmHg 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 purposes of this guideline is reported as mild or moderate pre-eclampsia.

Six RCTs were included in the review (n= 11,444 women). One multi-centre RCT (Magpie Trial 2002) 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 2002, few studies attempted to blind administration of the allocated treatment.

Women with severe pre-eclampsia

In severe pre-eclamptic women, magnesium sulphate was significantly better than none/placebo in preventing eclampsia (3 RCTs, N=3555: RR=0.37, 95% CI 0.22 to 0.64). No significant difference was found between the two groups in terms of maternal death, serious maternal morbidity, pulmonary oedema, placental abruption or kidney dialysis. Stillbirths and neonatal deaths rate was not 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 better than none/placebo in preventing eclampsia (4 RCTs, N=3889: RR=0.44: CI 0.28 to 0.69). Other outcomes, however, were not significantly different between the two groups (maternal death, serious maternal morbidity, stillbirth and neonatal deaths).

Follow-up for women (outcomes of 2 years)

One large RCT (Magpie trial)¹⁶³ [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 their original trial.¹⁶⁵ In the Magpie trial, 7927 women with pre-eclampsia before birth or 24 hours postpartum (DBP \geq 90 mmHg, SBP \geq 140 mmHg, \geq 1+ proteinuria) were randomised to receive either magnesium sulphate (intravenous or intramuscular) or identical placebo regimens. 4782 women were ultimately included in the follow-up study of which 3,375 responded (reasons for exclusions included the feasibility of following up in some centres, women discharged without a surviving child, and women who opted out of centres that contacted less 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 significant difference in the primary outcome was found between the two groups (58/1650 versus 72/1725: RR=0.84, 95% CI 0.60 -1.18). This difference stayed insignificant when 'death' and 'serious morbidity' outcomes were analysed separately. Subgroup analyses were conducted for the primary outcome to see if the results were affected by the severity of pre-eclampsia (severe versus mild-moderate), the randomisation (before versus after delivery) or the countries' 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 – 2.16).

Follow-up for children (outcomes of 18 months)

In another publication¹⁶⁴ from the Magpie trial, 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). 4483 children were contacted of whom 3283 ultimately participated in this follow-up study (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 significant difference in the primary outcome was found between babies born to mothers treated with magnesium sulphate or placebo (245/1635 versus 233/1648: RR= 1.10, 95% CI 0.93 – 1.29). The difference stayed insignificant when 'death' and 'neurosensory disability' outcomes were analysed separately (death: 226/1635 versus 206/1648: RR=1.06, 95%CI 0.90-1.25; neurosensory disability 10/1409 versus 27/1442: RR=0.72, 95% CI 0.40- 1.29).

Subgroup analyses were conducted for the primary outcome to see if the results were affected by the severity of pre-eclampsia at trial entry (severe, moderate, mild), gestation at birth (≤ 33 wks, > 33 wks) or the country's perinatal mortality index (high, middle, low). Results were consistent across all subgroups.

No significant difference was 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 met the inclusion criteria¹⁶⁶ by Simon et al 2006. The study was a multinational trial-based economic evaluation, Magnesium Sulphate for Prevention of Eclampsia (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 co-ordinated 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 GDG then reported this figure in GBP 2009 prices using a CPI conversion calculator.¹⁶⁷ Cost effectiveness was estimated for three categories of countries grouped by gross national income (GNI) into high, middle and low GNI countries using a regression model. Uncertainty was explored using probabilistic sensitivity analyses. We abstracted results of the high income countries which are relevant to the UK.

Using magnesium sulphate to prevent eclampsia in women with pre-eclampsia cost, on average, \$86 (approximately £60) and resulted 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 was 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 health care 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. 80% 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, £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 well presented. Although NICE's preferred measure of outcome is a QALY the study did not consider this; however we believe this approach would be unlikely to change the conclusions of the analysis since eclampsia is a good proxy for both quality and quantity of life which 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 significantly better than no treatment/placebo in preventing eclampsia. However, there was no significant difference in other outcomes including maternal death and serious maternal morbidity.

One 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 significant difference 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 significance was 'gynaecological problems' for which the risk was higher in the magnesium group. No significant difference was found for the babies any of the other studied outcomes (isolated speech delay or significant disability).

Treatment of eclampsia

Three Cochrane systematic reviews studied the use of magnesium sulphate in women with eclampsia compared with diazepam¹⁵⁹, phenytoin¹⁶⁰ and lytic cocktail (lytic cocktail is no longer used in UK clinical practice).¹⁶¹ 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 review¹⁵⁹ [EL=1++] investigated the effects of magnesium sulphate (intramuscular or intravenous) when compared with diazepam. Participants were women with eclampsia at trial entry before or after delivery, had singleton or multiple pregnancies, and may have had an anticonvulsant before trial entry.

Seven RCTs were included in the review (n=1,441 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),¹⁶⁸ 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 significantly less in the magnesium sulphate group in comparison with the diazepam ones (maternal death: 6RCTs, N=1336: RR=0.59, 95% CI 0.37 to 0.94; recurrence of convulsions: 7RCTs, N=1441: RR=0.44, 95% CI 0.34 to 0.57), (Table 10.1a).

Babies for women treated with magnesium sulphate were significantly less likely to stay in special care baby units (SCBU) >7days (3RCTs, N=718: RR=0.66, 95% CI 0.46 to 0.95) and to be intubated at place of birth (2RCTs, N=591: RR=0.67, 95% CI 0.45 to 1.00) when compared with babies born to diazepam-treated mothers. Besides, magnesium sulphate babies were significantly less likely to score <7 in Apgar scale measured at both 1-minute (2RCTs, n=597: RR=0.75, 95% CI 0.65 to 0.87) and 5-minutes after delivery (2RCTs, N=597: RR=0.72, 95% CI 0.55 to 0.94), (Table 10. 2).

Magnesium sulphate versus phenytoin

A Cochrane systematic review¹⁶⁰ [EL=1++] investigated the effects of magnesium sulphate (intramuscular or intravenous) when compared with phenytoin. Participants were women with eclampsia at trial entry either before or after delivery, had singleton or multiple pregnancies, and 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).¹⁶⁸ 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 significantly less in the magnesium sulphate group compared to the phenytoin group (five RCTs, N=895: RR=0.31, 95% CI 0.20 to 0.47). Women in the magnesium sulphate group were 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 less likely to be given supportive mechanical ventilation (one RCT, N=775: RR=0.66, 95% CI 0.49 to 0.90), (Table 10.1).

Babies born to women treated with magnesium sulphate were significantly less likely to be admitted to special care baby units (one RCT, n=518, RR 0.73, 95% CI 0.58 to 0.91) and were significantly less likely to either die or to be admitted to special care baby units 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 magnesium sulphate treated women compared with those treated with phenytoin scored <7 in Apgar at 1-minute (1RCT, N=518: RR=0.78, 95% CI 0.66 to 0.93). However, the Apgar score <7 at 5-minutes did not show significant difference, (Table10. 2).

Magnesium sulphate versus lytic cocktail

A Cochrane systematic review¹⁶¹ [EL=1++] investigated the differential effects of magnesium sulphate (intramuscular or intravenous) when compared with any

combination of drugs known as 'lytic cocktail' regardless of their constituents or how they were administered. Participants had eclampsia at trial entry which could have been before or after delivery, had singleton or multiple pregnancies, and 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 significantly less in the magnesium sulphate group compared with the phenytoin group (2RCTs, N=198: RR=0.09, 95% CI 0.03 to 0.24). Women in the magnesium sulphate group had significantly less cases of coma at >24 hours and respiratory depression [(1RCT, N=108: RR=0.04, 95% CI 0.00 to 0.74) and (2RCTs, N=198: RR=0.12, 95% CI 0.02 to 0.91), respectively], (Table. 1). Fetal or infant deaths were significantly lower in the magnesium sulphate group (2RCT, N=177: RR=0.45, 95% CI 0.26 to 0.79), (Table 10. 2).

Table 10.1a Magnesium sulphate for eclampsia (maternal outcomes)

Maternal outcomes	Evidence	Maternal death	Recurrence of convulsions	Admission to ICU	Coma > 24 hrs	Respiratory depression	Pulmonary oedema	Pneumonia	Mechanical ventilation	Renal failure	Stroke	HELLP syndrome	Placental abruption	Cardiac arrest
MgSO4 versus diazepam [EL 1++]	Cochrane review ¹⁵⁹ 7RCTs, N=1441	6RCTs, N=1336: RR=0.59 (0.37 - 0.94)	7RCTs, N=1441: RR=0.44 (0.34 - 0.57)	2RCTs, 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, (10.33 - 1.23)	-	-	3 RCTs, N=1025: RR=0.94 (0.47 - 1.88)
MgSO4 versus phenytoin [EL 1++]	Cochrane review ¹⁶⁰ 6RCTs, N=897	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)	-	-	1RCT, N=775: RR=1.16 (0.39 - 3.43)
MgSO4 versus lytic cocktail [EL 1++]	Cochrane review ¹⁶¹ 2RCTs, N=199	-	2 RCTs, N=198: RR=0.09 (0.03 - 0.24)	-	1 RCT, N=108: RR=0.04 (0.00- 0.74)	2 RCT, 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)

Shaded cells indicate significant effects (at the 5% level)

Table10.1b. Magnesium sulphate for eclampsia (fetal outcomes)

Fetal Outcome s	Evidence	Death of fetus or infant			Utilisation of SCBU		Death in SCBU > 7days	Intubation at place of birth	Apgar score	
		Stillbirth	Perinatal death	Neonatal death	Admission	Stay > 7 days			<7 at 1-min	<7 at 5-min
MgSO4 versus diazepam [EL 1++]	Cochrane review ¹⁵⁹ 7RCTs, N=1441	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)
MgSO4 versus phenytoin[EL 1++]	Cochrane review ¹⁶⁰ 6RCTs, N=897	2RCTs, N=665: RR=0.83(0.61- 1.13)	2RCTs,N=665: RR=0.85, 95% CI 0.67 to 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)
MgSO4 versus lytic cocktail [EL 1++]	Cochrane review ¹⁶¹ 2RCTs, N=199	2RCTs, 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)						

Shaded cells indicate significant effects (at the 5% level)

Evidence statement

A Cochrane review [EL=1++] showed that in women with eclampsia, magnesium sulphate had significantly better results than diazepam in preventing maternal death and recurrence of convulsions. Babies of women treated with magnesium sulphate were significantly less likely to stay in SCBU > 7days, to be intubated at place of birth or have an Apgar score less than 7 at both 1-min and 5-min from delivery.

A Cochrane review [EL=1++] showed that in women with eclampsia, magnesium sulphate has significantly better results than phenytoin in preventing recurrence of convulsions. They were also significantly less likely to be admitted to ICU or to be given supportive mechanical ventilation. No significant results were found between the two groups in preventing maternal death. Babies born to women treated with magnesium sulphate were significantly less likely to be admitted to SCBU, to stay there for more than 7days or to die there after > 7days.

A Cochrane review [EL=1++] showed that in women with eclampsia, magnesium sulphate has significantly better results than a cocktail of lytic agents in preventing recurrence of convulsion, having a coma >24hrs or respiratory depression. Fetal or infant deaths were 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 mild to moderate pre-eclampsia 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 reduced the incidence of further eclamptic fits. There was also clear evidence from systematic reviews that magnesium sulphate was 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.¹⁶⁸ The GDG's view is that the regimen for administration of magnesium sulphate should be the intravenous regimen used in the Collaborative Eclampsia Trial,¹⁶⁸ 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 Trial¹⁶⁸ 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.^{159 160}

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 clinical features of severe pre-eclampsia:

- hypertension and proteinuria and
- symptoms of severe headache or
- problems with vision, such as blurring or flashing before the eyes or
- severe pain just below the ribs or vomiting or
- papilloedema or
- signs of clonus (≥ 3 beats)
- liver tenderness or
- HELLP syndrome or
- platelet count falling to below 100×10^9 per litre or
- 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.

10.3 Antihypertensives

Clinical effectiveness

The population considered here includes 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 which compared different antihypertensive agents.¹⁶⁹⁻¹⁷⁶

One of these studies was a Cochrane systematic review¹⁶⁹ [EL 1++] of all randomised trials (quasi-random designs were excluded) which 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 (DBP ≥ 105 mmHg and/or SBP ≥ 160 mmHg) 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 which (n=1750) compared nimodipine with magnesium sulphate.

The antihypertensive drugs evaluated in these trials were hydralazine, calcium channel blockers (nifedipine, nimodipine, nicardopine and Isradipine), labetalol, methyldopa, diazoxide, prostacyclin, 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 (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 prostacyclin), (labetalol versus methyldopa, calcium channel blockers or diazoxide), (magnesium sulphate versus nitrates or Nimodipine) and (nifedipine versus chlorpromazine).

6 other trials were identified which were not included in the Cochrane review four were [EL=1+] ^{171;174-176} and two [EL=1-] ^{172;173}. These trials studied 5 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 ¹⁷⁰ [EL=1++] which compared hydralazine with other antihypertensive drugs in pregnant women with moderate to severe hypertension (DBP:100-109 mmHg moderate, ≥110 mmHg severe). 21 RCTs were included (n=1085 women). Randomisation method was adequate in 11 trials while it was unknown or inadequate in the other trials. Blinding was applied in 4 trials. The other 17 were either not blinded (n=11) or blinding was not reported (n=6). Five of these studies had women with moderate hypertension [1x labetalol versus hydralazine (n=30), 2x urapidil versus hydralazine (n=59) and 2x ketanserin versus hydralazine (n= 100)].

The meta-analysis identified five comparisons (labetalol, calcium channel blockers or ketanserin or urapidil or prostacyclin 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 anti-hypertensive 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. Tables 10.3 to 10.9 present comparisons based on evidence available from two or more difference sources (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

Cochrane review (3 RCTs, N=69) [EL=1++] ¹⁶⁹:

No significant differences were found between the two drugs.

Meta-analysis (5 RCTs, N=156) [EL=1++] ¹⁷⁰:

Women treated with labetalol were significantly more likely to have persistent high blood pressure in comparison with hydralazine (4RCTs, N=126: RR=3.4, 95%CI 1.0 – 12.5). However, they were less likely to have hypotension (4RCTs, N=122: RR=0.2, 95% CI 0.0 – 0.9) or to suffer from side effects (5RCTs, N=156: RR=0.3, 95% CI 0.2 – 0.6).

Individual RCT (N=200: 100 each arm) [EL=1+] ¹⁷¹:

This is a non-blinded randomised trial from Panama. The study included 200 women with severe hypertension (BP ≥ 160/110 mmHg), at ≥ 24 weeks 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 max dose of 300 mg (five doses). Hydralazine was given intravenously (5 mg slow bolus) and repeated every 20 minutes up to a max of 5 doses.

The study showed no 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

Cochrane review (6RCTs, N=313) [EL=1++] ¹⁶⁹:

Women treated with calcium channel blockers were significantly less likely to have persistent high blood pressure than those treated with hydralazine (5RCTs, N=263: RR=0.33, 95% CI 0.15 – 0.70). No other significant differences were found.

Meta-analysis (9 RCTs, N=619) [EL=1++] ¹⁷⁰:

Babies born to women treated with calcium channel blockers were significantly less likely to have fetal heart rate decelerations than those born for women treated with hydralazine (6RCTs, N=360: RR=0.2, 95% CI 0.1 to 0.6). No other significant differences were found.

Individual RCTs

Nifedipine versus hydralazine (N=79: 49 each arm) [EL=1-] ¹⁷²:

This is a non-blinded quasi-randomised trial (women numbered as they attended: even numbers/hydralazine, odd numbers/nifedipine) from Ghana. The study included 79 women with severe pre-eclampsia (BP \geq 160/110 mmHg, proteinuria \geq 1+), who were \geq 28 weeks. Nifedipine was given sublingually (10 mg capsule). This was repeated every 30 min if BP was \geq 160/110 mmHg. After that, 10 mg tablets were given orally every 6-8 hrs until delivery. Hydralazine was given intravenously (5 mg bolus) and was repeated at intervals determined by blood pressure measurements. When diastolic pressure stabilised around 90-100 mmHg, 20-80 mg hydralazine tablets in divided doses were administered until delivery.

The study showed women on nifedipine were significantly less likely to develop persistent high blood pressure than women treated with hydralazine (RR=0.28, 95% CI 0.11 – 0.71). No other significant results were found.

Isradipine versus hydralazine (N=39: 20 versus 19) [EL=1-] ¹⁷³:

This is a small non-blinded quasi-randomised trial from Jamaica. The study included 39 women with severe pre-eclampsia (BP \geq 160/110 mmHg, proteinuria \geq 1+), who were \geq 28 weeks. Isradipine was infused 0.15g/kg/min over 6 hours to a total max dose of 2.8 mg. When diastolic pressure was controlled below 100 mmHg, slow release tablets (5mg, twice a day) was started. Hydralazine was infused (2mg/kg/h) to a max of 20 mg followed by oral alpha-methyldopa 500 mg three times a day.

The study only reported one outcome (caesarean section) which showed no significant difference between the two groups.

Ketanserin versus hydralazine

Cochrane review (4RCTs, N=200) [EL=1++] ¹⁶⁹:

Women treated with ketanserin were significantly more likely to have persistent high blood pressure than those treated with hydralazine (3RCTs, N=180: RR=4.79, 95% CI 1.95 – 11.73). However, they were significantly less likely to suffer adverse effects from the drug (3RCTs, N=120: RR=0.32, 95% CI 0.19 to 0.53) or to develop

HELLP syndrome (1RCT, N=44: RR=0.20, 95% CI 0.05 – 0.81). No other significant differences were found.

Meta-analysis (4RCTs, N=190) [EL=1++]¹⁷⁰:

Women treated with ketanserin were significantly less likely to suffer from adverse effects than those treated with hydralazine (2RCTs, N=64: RR=0.4, 95% CI 0.2 – 0.7). No other significant differences were found.

Urapidil versus hydralazine

Cochrane review (2RCTs, N=59) [EL=1++]¹⁶⁹:

No significant differences were found.

Meta-analysis (2RCTs, N=59) [EL=1++]¹⁷⁰:

No significant differences were found.

Prostacyclin versus hydralazine

Cochrane review (1RCT, N=47) [EL=1++]¹⁶⁹:

No significant differences were found.

Meta-analysis (1RCTs, N=47) [EL=1++]¹⁷⁰:

No significant differences were found

Labetalol versus calcium channel blockers

Cochrane review (1RCT, nifedipine N=60) [EL=1++]¹⁶⁹

No significant differences were found.

Individual RCT:¹⁷⁴ [EL=1+] (N=50, nifedipine 25 each arm)

This was a double-blind RCT (computer generated randomisation) from the USA. Women (≥ 24 weeks) with severe pre-eclampsia or chronic hypertension with superimposed pre-eclampsia, either intrapartum (n=29) or within 24 h postpartum (n=21) were included. Severe hypertension was defined as sustained systolic blood pressure ≥ 170 mmHg or diastolic blood pressure ≥ 105 mmHg on repeat measurements 15 minutes apart. Women were randomly assigned to receive either nifedipine or labetalol. Nifedipine was given orally (10 mg) with repeated doses of 20 mg every 20 minutes for up to a maximum of 5 doses. Labetalol was given intravenously (20 mg) followed by escalating doses of 40 then 80 until a maximum of 5 doses.

The study showed no significant differences in side effects, Apgar score <7 at 5 minutes or umbilical artery pH < 7.0 between the two groups.

Labetalol versus methyldopa

Cochrane review (1RCT, N=74) [EL=1++]¹⁶⁹:

No significant differences were found.

Labetalol versus diazoxide

Cochrane review (1RCT, N=90) [EL=1++]¹⁶⁹:

Women treated with labetalol were significantly less likely to have maternal hypotension than those treated with diazoxide (1RCT, N=90: RR=0.06, 95% CI 0.00 – 0.99). No other significant differences were found.

Nitrates versus magnesium sulphate

Cochrane review (1RCT, N=36) [EL=1++]¹⁶⁹:

No significant differences were found.

Nifedipine versus chlorpromazine

Cochrane review (1RCT, N=60) [EL=1++] ¹⁶⁹:

No significant differences were found.

Nifedipine versus prazosin

Cochrane review (1RCT, N=130) [EL=1++] ¹⁶⁹:

No significant differences were found.

Nimodipine versus magnesium sulphate

Cochrane review (2RCT, N=1683) [EL=1++] ¹⁶⁹:

Women treated with nimodipine were significantly less likely to develop persistent high blood pressure than those treated with magnesium sulphate (1RCTs, N=1650: RR=0.84, 95% CI 0.76 – 0.93). For specific side effects, women treated with nimodipine were significantly less likely to report 'flushing' than those treated with magnesium sulphate (1RCT, N=1650: RR=0.22, 95% CI 0.12 to 0.40). No other significant differences were found.

Diazoxide versus hydralazine

Individual RCT: ¹⁷⁵[EL=1+] (N=97, 50 versus 47):

This was a randomised trial from Australia. Women requiring intravenous antihypertensive treatment (97 antenatal period, 27 postnatal period) were randomised to receive either diazoxide (15 mg boluses/3min until pressure is controlled or 300 mg is given) or hydralazine (5mg boluses every 20 min for up to three doses). Four cases in each group were prescribed two oral medications before and after the administration of i.v medications. Authors reported 24 drug administration protocol violations.

The study showed no significant differences between the two studied groups.

Nitroglycerine versus nifedipine

Individual RCT: ¹⁷⁶ [EL=1+] (n=32, 16 each arm)

This was a double blind RCT from Mexico. Women (\geq 24 weeks) with uncomplicated severe pre-eclampsia, and 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 μ g/minute) with increases in dose of 5 μ g/min every 5 minutes or nifedipine capsules (10 mg) every 30 minutes. Both groups received a loading dose of magnesium sulphate 4g/250 ml dextrose 5% in water (D5W) intravenously followed by an i.v infusion of 1g/h for up to 8 hours postpartum.

The study showed no significant differences in side effects, caesarean sections, post-delivery bleeding > 1000 ml or Apgar score <7 at 1-min and 5 min between the two groups.

Table 10.2. Source and level of evidence for comparisons between the different agents

	Hydralazine	Labetalol	Ca blockers	Ketanserin	Urapidil	Prostacyclin	Diazoxide	Methyldopa	Nitrates	Chlorpromazine
Hydralazine	N/A	C [EL 1++] M [EL 1++] I [EL 1+]	C [EL 1++] M [EL 1++] I 2x[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 2x[EL 1-]	C [EL 1++] I [EL 1+]	N/A	-	-	-	-	-	I [EL 1+]	C [EL 1++]
Magnesium sulphate	-	-	C [EL 1++]	-	-	-	-	-	C [EL 1++]	-

Table 10.3. Labetalol versus hydralazine, evidence: Cochrane review, meta-analysis and individual trials

Labetalol versus hydralazine	Total number of RCTs & 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	Admission to NICU
Cochrane ¹⁶⁹ [EL 1++]	3RCTs, N=69	1RCT, N=20 no cases	1RCT, N=20: RR=3.00 (0.79-11.44)	2RCTs, N=50 no cases	2RCTs, N=50: RR=0.52 (0.24 -1.11)	3RCTs, N=69: RR=0.71 (0.40 - 1.24)				3RCTs, N=69: RR=0.84 (0.01- 54.78)	3RCTs, N=69: RR=0.50 (0.05-4.94)	1RCT,N=19: RR=0.69(0.15- 3.12)	At 5-min: 1RCT, N=19: RR=0.10 (0.01- 1.81)		Neonatal hypoglycaemia : 2RCTs, N=39: RR=1.14 (0.19 -6.94)
Magee et al ¹⁷⁰ [EL 1++]	5RCTs, N=156	-	4RCTs, N=126: RR=3.4 (1.0, 12.5)	4RCTs, N=122: RR=0.2 (0.0, 0.9)	5RCTs, N=156: RR=0.3 (0.2, 0.6)	-					Stillbirth: 5 RCTs, N=109: RD= -0.05(-0.17 to +0.08)	-	-		
Vigil-De et al ¹⁷¹ [EL 1+] Country : Panama	Individual RCT, N=200	100 versus 100 no cases	5/100 versus 5/100 RR=1.00 (0.30, 3.35)	0/100 versus 2/100, NS	18/100 versus 10/100, RR=1.80 (0.87, 3.70)	56/100 versus 51/100, RR=1.10 (0.85, 1.42)	1/100 VS. 2/100, NS	1/100 versus 0/100, NS	HELLP Syndrome: 2/100 versus 2/100, RR=1.0 (0.14 to 6.96)	6/103 versus 8/102, RR=0.74 (0.27, 2.06)	2/103 versus 2/102, NS	26/103 versus 23/102, RR=1.12 (0.69, 1.83)	At 1-min: 20/103 versus 14/102, RR=1.41 (0.76, 2.64) At 5-min:4/103 versus 2/102, RR=1.98 (0.37 to 10.57)	32/103 versus 32/102 RR=0.99 (0.66, 1.49)	Neonatal complications: 29/103 versus 27/102, RR=1.06 (0.68, 1.66)

Table 10.4 Calcium channel blockers versus hydralazine, evidence: Cochrane review, meta-analysis and individual trials

Ca blockers versus hydralazine	Total number of RCTs & 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 ¹⁶⁹ [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)*	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 ¹⁷⁰ [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 ¹⁷² [EL 1-], nifedipine Country : Ghana	Individual RCT, N=79	–	5/44 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 ¹⁷³ [EL 1-], isradipine Country: Jamaica	Individual RCT, N=39	–	–	–	–	3/20 versus 2/19 RR=1.43 (0.27, 7.61)				–	–	–	–		
<p>*Specific side effects: Palpitations: 2 RCTs, N=87: RR=0.63, 95%CI 0.29 to 1.39 Nausea and/or vomiting: 3 RCTs, N=120: RR=3.48, 95%CI 1.01 to 11.99 Headache: 4 RCTs, N=246: RR=1.09, 95%CI 0.50 to 2.36 Flushing: 3 RCTs, N=120: RR=2.26, 95%CI 0.83 to 6.13 Dyspnoea: 1 RCT, N=37: RR=0.85, 95%CI 0.06 to 12.59</p>															

Table 10.5 Ketanserin versus hydralazine, evidence: Cochrane review and meta-analysis

Ketanserin versus hydralazine	Total number of RCTs & participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effect 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 ¹⁶⁹ [EL 1++]	4RCTs, N=200	2RCTs, 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)	2RCTs, N=64: RR=0.14, 95%CI 0.02 to 1.10	1RCT, N=44: RR=0.11 (0.01 - 1.95)	Maternal death: 2RCTs, N=124: RR=0.32, 95%CI 0.03 to 2.96 Severe morbidity: 1RCT, N=56: RR=0.32 (0.09 -1.12) HELLP syndrome: 1RCT, N=44: RR=0.20 (0.05 -0.81)	-	2 RCTs, N=116: RR=0.27 (0.05 - 1.64)	-	-	-	-
Magee et al ¹⁷⁰ [EL 1++]	4RCTs, 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)	-	-	-	-

Table 10.6 Urapidil versus hydralazine, evidence: Cochrane review and meta-analysis

Urapidil versus hydralazine	Total number Of RCTs & 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 ¹⁶⁹ [EL 1++]	2RCTs, N=59	1RCT, N=26 no cases	2, N=59: RR=1.38 (0.06-31.14)	1, N=33: RR=0.22 (0.02 - 2.13)	2, N=59: RR=0.59 (0.10 -3.58)	2,N=59: RR=0.77 (0.51 -1.16)	1RCT, N=33: RR=0.15 (0.01 - 3.46)	-	-	-	Stillbirth: 1RCT, N=26 no cases Neonatal death: 2, N=59: RR=0.66 (0.08-5.25)	-	-	-	-
Magee et al ¹⁷⁰ [EL 1++]	2RCTs, N=59	-	2, N=26 no cases	1, N=33: RR=0.2 (0.0, 2.1)	1RCT, N=29: RR=1.4 (0.2, 11.1)	-	-	-	-	2, N=55: RR= 0.1 (0.0, 1.8)	Stillbirth: 2, N=56 no cases	-	-	-	-

Table 10.7 Prostacyclin versus hydralazine, evidence: Cochrane review and meta-analysis

Prostacyclin versus hydralazine	Total number of RCTs & 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 ¹⁶⁹ [EL 1++]	1RCT, N=47		1RCT, N=47: RR=0.23, (0.01 -4.47)	-	1RCT, N=47: RR=1.14 (0.08 - 17.11)	1RCT, N=47: RR=0.74 (0.50- 1.10)	-	-	-	-	1RCT, N=47: RR=1.14 (0.08 -17.11)	-	-	-	Ventilation: 1RCT, N=47: RR=0.32 (0.08 -1.80)
Magee et al ¹⁷⁰ [EL 1++]	1RCT, N=47		1RCT, N=50: RR=0.2 (0.0, 4.5)	-	-	-	-	-	-	1RCT, N=47: RR=0.9 (0.5, 1.5)	Stillbirth: 1RCT, N=47 no cases	-	-	-	-

Table 10.8 Labetalol versus calcium channel blockers, evidence: Cochrane review and individual RCTs

Labelalol Vs. calcium channel blockers	Total number of RCTs & 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 ¹⁶⁹ (Nicardopine)	1RCT, N=60	1,N=60: RR=1.22 (0.59- 2.51)	-	1, N=60 no cases	* Specific side effects	-	-	-	-	-	-	-	-	-	-
Vermillion et al ¹⁷⁴ (Nifedipine) Country: USA	Individual RCT, N=50 [EL 1+]	-	-	-	** Specific side effects	-	-	-	-	-	-	-	At 5-min: 2/14 versus 1/15, NS	-	Umbilical artery pH <7.0: 1/15 versus 1/14, RR=1.07 (0.07, 15.54)
<p>* Specific side effects: Nausea and/or vomiting: 1RCT, N=60: RR=1.00, 95% CI 0.07 to 15.26 Palpitation: 1RCT, N=60: RR=0.14, 95% CI 0.01 to 2.65 **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</p>															

Table 10.9 Different antihypertensives comparisons, evidence: Cochrane review

	Total number of RCTs & participants	Eclampsia	Persistent high blood pressure	Maternal hypotension	Side effects for the women	Caesarean section	Placental abruption	Pulmonary Oedema	Other maternal outcomes	Fetal hear rate deceleration	Fetal or neonatal death	Respiratory distress syndrome	Appgar < 7	Admission to NICU	Others
Labetalol versus methyldopa Cochrane ¹⁶⁹	1RCT, N=74		1, N=72: RR=1.19 (0.74 -1.94)	-	-	1, N=72: RR=0.85 (0.56-1.30)	-	-	-	-	1, N=72: RR=4.49 (0.22 -90.33)	-	-	1RCT, N=72: RR=1.06 (0.66-1.71)	Small for gestation: 1RCT, N=72: RR=0.43 (0.43 -
Labetalol versus diazoxide Cochrane ¹⁶⁹	1RCT, N=90		1, N=90: RR=0.50 (0.130 - 1.88)	1, N=90: RR=0.06 (0.00 - 0.99)	-	1, N=90: RR=0.43 (0.18-1.02)	-	-	-	-	1, N=90: RR=0.14 (0.01-2.69)	-	-	-	-
Nitrates versus MgSO4 Cochrane ¹⁶⁹	1RCT, N=36	1, N=36 no cases	1, N=36: RR=0.14, (0.01- 2.58)	-	-	1, n=36: RR=0.19 (0.07-0.53)	-	-	-	-	-	-	-	-	-
Nifedipine versus chlorpromazine Cochrane ¹⁶⁹	1RCT, N=60	1, N=55: RR=2.52 (0.11-59.18)	1, N=60: RR=0.09 (0.01 -1.57)	-	-	1, N=55: RR=0.80 (0.60- 1.05)	1RCT, N=1650: RR=0.76 (0.27 - 2.18)	-	Stroke: 1RCT, N=1650 no cases.	-	-	-	-	-	Baby in delivery: N=1650: RR=0.76 (0.76 - 1.09)
Nifedipine versus prazosin Cochrane ¹⁶⁹	1RCT, N=130	1, N=145 no cases	-	-	-	1, N=145: RR=0.90 (0.72 to 1.13)	1RCT, N=145: RR=0.96 (0.40- 2.28)	1RCT, N=145: RR0.19 (0.02- 1.60)	HELLP Syndrome: 1RCT, N=145: RR=0.48 (0.04- 5.17) Renal Failure: 1RCT, N=145: RR=0.48 (0.04- 5.17)	-	1RCT, N=149: RR=0.46 (0.18 - 1.13)	1RCT, n=130: RR=1.22 (0.52- 2.82)	-	1RCT, N=130: RR=0.78 (0.49 - 1.23)	-
Nimodipine versus MgSO4 Cochrane ¹⁶⁹	2RCTs, N=1683	2, N=1683: RR=2.24 (1.06- 4.73)	1, N=1650: RR=0.84 (0.76 - 0.93)	1, N=1650: RR=0.72, (0.23- 2.27)	**Specific side effects	2, N=1683: RR=0.97 (0.89-1.06)	-	-	-	-	-	-	-	-	-

** Specific side effects:
 Headache: 1RCT, N=1650: RR=1.06, 95% CI 0.71 to 1.58
 Flushing: 1RCT, N=1650: RR=0.22, 95% CI 0.12 to 0.40
 Nausea and/or vomiting: 1RCT, N=1650: RR=0.86, 95% CI 0.59 to 1.24

Table 10.10 Different antihypertensives comparisons, evidence: individual RCTs

	Total number of RCTs & 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 ¹⁷⁵ Country: 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-min: 4/52 versus 4/49 RR=0.94 (0.25, 3.56)	–	Neonatal hypoglycaemia: 6/52 versus 5/49 R=1.13 (0.37, 3.47)
Nitroglycerine versus nifedipine Manzur-Verastegui et al ¹⁷⁶ Country: Mexico	Individual RCT, N=32 [EL 1+]	–	–	–	* Specific side effects	11/16 versus 12/16 RR=0.92 (0.59, 1.42)	–	–	Post-delivery bleeding > 1,000 ml: 1/16 versus 3/16, RR=0.33 (0.04, 2.88)	–	16 versus 16, no cases	–	At 1-min: 2/16 versus 7/16, NS At 5-min: 1/16 versus 0/16, NS	–	–
*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 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 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 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 significantly less likely to have fetal heart decelerations than those treated with hydralazine. No other significant results were found.

Ketanserin versus hydralazine

The Cochrane review [EL=1++] showed that women treated with ketanserin were 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 significantly less likely to have side effects. No other results were significantly different between the two groups.

Urapidil versus hydralazine

Both the Cochrane review [EL=1++] and the meta-analysis [EL=1++] showed no significant differences between the two groups in the primary and secondary outcomes.

Prostacyclin versus hydralazine

Both the Cochrane review [EL=1++] and the meta-analysis [EL=1++] showed no 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 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 significantly less likely to develop hypotension than those treated with methyldopa. No other significant differences were found.

Labetalol versus methyldopa

The Cochrane review showed no significant differences between the two groups in the primary and secondary outcomes.

Nitrates versus magnesium sulphate

The Cochrane review showed no significant differences between the two groups in the primary and secondary outcomes.

Nifedipine versus chlorpromazine

The Cochrane review showed no significant differences between the two groups in the primary and secondary outcomes.

Nifedipine versus prazosin

The Cochrane review showed no 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 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 significant differences were found.

Diazoxide versus hydralazine

Individual RCT [EL=1+] showed no significant difference in primary and secondary outcomes between the two groups.

Nitroglycerine versus nifedipine

Individual RCT [EL=1+] showed no 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 anti-hypertensive 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 500ml 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 recommendations

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 review¹⁷⁷ [EL=1++] investigated the effect of antenatal corticosteroids for accelerating fetal lung maturation in women at risk of preterm birth. 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 which 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 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 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 in women with pregnancies complicated by hypertensive syndromes.

A large non-randomised retrospective study has suggested that babies exposed to betamethasone antenatally have less neonatal cystic periventricular leukomalacia than those exposed to antenatal dexamethasone.¹⁷⁸ [EL= 2-] Another historical cohort study reported a statistically significant reduction in the number of neonatal deaths with the use of dexamethasone compared to betamethasone (OR 1.66, 95% CI 1.07 to 2.57, p<0.05).¹⁷⁹ [EL= 2-]

Evidence statement

A Cochrane review [EL=1++] showed that the antenatal corticosteroids in women with hypertensive syndromes significantly reduced the risk of neonatal death, respiratory distress syndrome and intraventricular 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 leukomalacia) than was 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 prematurity, 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 leukomalacia); the two drugs are similarly priced and so the recommendation to use betamethasone is likely to be cost effective.

In formulating their 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.¹⁸⁰

Recommendations

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.

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 review¹⁸¹ [EL=1++] studied two comparisons: dexamethasone plus standard treatment versus standard treatment alone and dexamethasone versus betamethasone. One additional RCT¹⁸² [EL=1+] compared dexamethasone with placebo while another RCT¹⁸³ [EL=1+] compared the use of dexamethasone and betamethasone.

Dexamethasone plus standard treatment versus standard treatment alone

A Cochrane review¹⁸¹ [EL=1+] investigated the effects of corticosteroids in women with HELLP syndrome (diagnosed clinically and by biochemical parameters) during pregnancy or shortly after delivery. All RCTs and trials which 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 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, renal failure or placental abruption). There was no significant difference 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 difference was found in postpartum sepsis, caesarean sections and increase in platelet count over 48 hours. However, there was a statistically significant difference in the mean number of hospital stay days post-randomisation (1RCT, N=30: WMD= -4.50, 95% CI -7.13 to -1.87) and time interval from randomisation to delivery (hrs) (1RCT, N=25: WMD=26.00, 95% CI 17.17 to 34.83), both of which were in favour of participants allocated to dexamethasone treatment.

A Colombian double-blind RCT¹⁸² [EL=1+] 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. 132 women were randomised to receive either dexamethasone (n=66) or placebo (n=66). The baseline characteristics of women in both groups were comparable. Randomisation was done by the use of stratified and random permuted blocks of 4, and concealment of allocation was ensured by using opaque envelopes. 10 mg i.v dexamethasone was given every 12 hours until delivery and 3 additional ones after delivery. Placebo group were given sterile water at a similar schedule.

There was no significant difference in maternal mortality between the two groups (3/66 versus 1/66: RR=3.0, 95% CI 0.32 to 28.1). There were also no significant differences between the two groups in maternal complications: acute renal failure, oliguria, pulmonary oedema, eclampsia, infections, and the need for platelets or plasma transfusion. Mean duration of hospitalisation of women was not significantly different between the two groups. No significant difference was found in the time to recovery of platelet counts (hazard ratio, 1.2: 95% CI 0.8 – 1.8), lactate dehydrogenase (hazard ratio 0.9, 95% CI 0.5 -1.50) or aspartate aminotransferase (hazard ratio 0.6, 95% CI 0.4 – 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 ¹⁸¹ [EL=1+] which made this comparison (N=40). No maternal death occurred. Perinatal mortality was not 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 abruptio placentae 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 participants randomised to dexamethasone. No significant difference was found in neonates need for ventilatory support or having respiratory distress syndrome. No cases of intracerebral haemorrhage and necrotising enterocolitis were recorded.

There was a statistically significant difference in favour of participants allocated to dexamethasone in the adjusted time-average change from baseline in the following secondary outcomes: the mean arterial pressure decrease (weighted mean deviation (WMD) -7.50, 95% CI -8.37 to -6.63), the mean increase in urinary output (WMD 24.80, 95% CI 19.58 to 30.02), the mean increase in platelet count (WMD 8.10, 95% CI 6.23 to 9.97), the mean decrease in lactate dehydrogenase activity (U/L) (WMD -54.20, 95% CI -88.22 to -20.18), the mean decrease in aspartate transaminase activity (U/L) (WMD -30.30, 95% CI -36.06 to -24.54).

The number of participants needing acute antihypertensive therapy in the dexamethasone group differed significantly statistically 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 regards to the number of neonates with a five minute Apgar less than, neonatal sepsis, neonatal hyperbilirubinaemia and mean time to discharge in days.

An American RCT ¹⁸³ [EL=1+] compared the efficacy of dexamethasone with betamethasone for the treatment of women with HELLP syndrome first manifesting itself in the postpartum period. Women who developed HELLP syndrome or any other manifestation of pre-eclampsia in the antepartum period were excluded. 36 women were randomised to receive either dexamethasone (10 mg intravenous every 12 hrs) (n=18) or betamethasone (12 mg IM every 24 hrs) (n=18). The baseline characteristics of women in both groups were comparable except for LDH level which was significantly higher in the dexamethasone group (1831.7 ± 1140.6 versus 1193.6 ± 496.4 U/l, 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 as 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 less antihypertensive treatment than the betamethasone group (1/18 versus 9/18: RR=0.11, 95% CI 0.02 to 0.79) and also had a decreased need for readmission to the obstetric recovery room (0/18 versus 4/18: 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 corticosteroid stayed in hospital for shorter periods and had shorter time intervals between randomisation and delivery. A RCT [EL=1+] also showed no difference in maternal or neonatal complication between women treated with corticosteroid 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 and betamethasone use in women with HELLP syndrome (antenatally or postnatally), a Cochrane review [EL=1+] showed no difference in the two groups in terms of maternal or neonatal complications. However, those treated with dexamethasone had higher time-average change in arterial pressure decrease, urinary output increase, platelet count increase, LDH and AST decrease. They were also less likely to need acute antihypertensive therapy. A 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 need readmission to 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.

Recommendations

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

Research recommendations

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 Netherlands¹⁸⁴ [EL=1+] investigated the use of a volume expansion protocol in women with severe hypertensive disorders of pregnancy (severe pre-eclampsia; HELLP syndrome, and concomitant fetal growth restriction) who presented with a viable singleton pregnancy at a gestational age between 24 and 34 weeks. Exclusion criteria included cases with 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 wks, between 30⁺⁰ and 33⁺⁶ wks) into either volume expansion group (n=111) or '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 both groups were comparable.

Volume-expansion group received 250 ml hydroxy-ethylstarch (HES) 6% x2 a day over 4h. Antihypertensives (i.v ketanserine) were used to achieve DBP 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% infused with medications in between the infusions of HES. Fluid treatment was discontinued if clinical signs of pulmonary oedema were observed.

Non-volume expansion group: antihypertensives (methyldopa) to achieve DBP between 95-105 mmHg. Additional medication (oral labetalol, nifedipine and intravenous ketanserin 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 IM betamethasone (2 doses of 11.4mg with 24h interval) was given when delivery was considered imminent before 32 wks of gestational age.

There was a trend towards a shorter pregnancy in the control group [7.4 (0.1 – 35) days versus 10.5 (0.2 – 440) days, $p=0.054$]. There was no difference in fetal or postnatal death. Live-born neonates for women in the volume expansion group were more likely to need ventilation or respiratory support (78/98 versus 60/98, RR=1.3, 95% CI 1.08 to 1.57). There was no difference in major maternal morbidity, but there were more caesarean sections in the treatment group (96/98 versus 88/98: RR=1.10, 95% CI 1.02 to 1.17). Neither neurological scores nor composite neonatal morbidity differed (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 higher in the treatment group (93/98 versus 80/98, RR= 1.26, 95% CI 1.05 to 1.30).

172 babies of participants of the previous RCT ($n=82$ treatment, $n=90$ control) were followed up for a year¹⁸⁵ [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 which includes two standardised development indices: Mental Development Index (MDI) and Psychomotor Development Index (PDI). Adverse neurodevelopmental infant outcome was defined as a MDI/PDI score <70 and/or an abnormal Touwen. 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 Bayley test nor was there a difference in the cases shown as suspect or abnormal in the Touwen test.

A Dutch case control study¹⁸⁶ [EL=2+] compared the results of nulliparous women with severe pre-eclampsia who were treated with a volume expansion protocol with those receiving none-volume-expansion treatment. 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 (max 1 week difference). Characteristics at admission for both groups were comparable.

The volume expansion group was admitted to ICU for central haemodynamic monitoring: If the PCWP <10 mmHg and/or cardiac index <3.5 l/min/m², women received i.v.i pasteurised plasma (250 ml/h) to maintain PCWP 10-12 mmHg and a cardiac index 3.5 - 4.6 l/min/m². If cardiac index was still <3.5 and DBP >100 mmHg, women received i.v.i dihydralazine (1mg/h), followed by hourly increments of 1mg. Methyldopa 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, diazepam where eclampsia was thought to be imminent or convulsions occurred; diet was unrestricted. Controls had bed rest, no intravenous fluids and a diet < 400 mg sodium/24 h. Women with symptoms of headache, upper abdominal pain or visual disturbances received Phenobarbital orally 30 mg t.i.d. Antihypertensive medication was given when DBP reached and remained ≥ 115 mmHg (iv dihydralazine). IV MgSO₄ was administered as anticonvulsant treatment.

No differences were found in prolongation of pregnancy between the two groups. Small-for-gestational-age infants (< 2.3 percentile) were significantly less frequent in the volume

expansion group than in controls (5/57 versus 19/57: OR=0.19, 95% CI 0.07 to 0.56). However, babies born to women in the volume expansion group were more likely to need artificial ventilation (27/57 versus 8/57: OR=5.51, 95% CI 2.22 to 13.70) and to have patent ductus arteriosus (9/57 versus 2/57: OR=5.16, 95% CI 1.06 to 25.04). Other neonatal complications were not different between the two groups. As for maternal complications, no differences were found in them for HELLP syndrome, abruptio placentae, pulmonary oedema, postpartum cardiomyopathy or postpartum renal insufficiency.

Evidence statement

In women with severe hypertension during pregnancy, a RCT [EL=1+] which compared women who received 'volume expansion' and those who received 'no volume expansion' treatment, showed no 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 differences were found in mental and psychomotor development of babies from the two groups. The use of volume expansion treatment was not different from none-volume expansion protocol in terms of fetal or postnatal death. Neither neurological scores nor composite neonatal morbidity differed between live-born neonates for women from the two groups. However, episodes of neonatal morbidity were higher in the treatment group. Babies born to women in the treatment group were more likely to need ventilation or respiratory support.

A case control study [EL=2+] showed no difference in prolongation of pregnancy between the two groups. As for maternal complications, no differences were found between the two groups. Small-for-gestational-age infants were significantly less frequent in the volume expansion group than in controls. However, babies born to women in the volume expansion group were more likely to need artificial ventilation and to have patent ductus arteriosus. Other neonatal complications were not 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 small for gestational age babies. There were no obvious maternal advantages.

The Confidential Enquiry into Maternal Deaths in the UK reported six deaths in 1994-6 due to adult respiratory distress syndrome (ARDS) that appeared to be related to poor fluid management in women with eclampsia or pre-eclampsia.¹⁸⁷ 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 2003-5 no deaths due solely to fluid mismanagement and ARDS were reported.¹⁸⁷

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

One Nigerian RCT¹⁸⁸ [EL=1-] compared caesarean section with labour induction in primigravida with singleton cephalic presentation and antenatal or imminent eclampsia and a closed cervical os. Fifty women were randomised to have caesarean section (n=25) or labour induction (n=25).

Labour was induced using misoprostol (50mg) and women were re-evaluated after 4 hours. If the woman went into labour another 50mg 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 > 110 mmHg.

Misoprostol failure was recorded in 4/25 (16%) women and they were subsequently delivered by caesarean section. The mean duration of admission was significantly longer in the caesarean section group (10.1 versus 6.08, p=0.05, no SD reported). There were no more maternal complications in the caesarean section group (8/25 versus 2/25: RR= 4.0, 95% CI 0.94 to 17.00). Apgar scores at 1 minute and 5 minutes, babies' admission to SCBU, perinatal mortality and maternal mortality did not differ between the groups.

An American retrospective cohort study¹⁸⁹ [EL=2+] looked at outcomes of infants born after labour induction in comparison with those delivered by caesarean section without labour. The study included 278 live-born 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 were significantly different in terms of age and nulliparity.

Both birthweight and gestation age were significantly lower in the CS group (birthweight (g): 1131 ± 232 versus 1235 ± 185, p, 0.001: gestation age (wks): 29.9 ± 2.3 versus 30.8 ± 2.6, p=0.004). After adjustment for birth weight and gestation age, logistic regression analysis showed the OR for Apgar score ≤3 at 5-min to be significantly different (Induction group: OR=6.1, 95% CI 1.1 to 32.2). The ORs for umbilical artery blood pH ≤ 7.0, respiratory distress, sepsis, intraventricular haemorrhage, seizures and neonatal deaths were not significant.

Vaginal birth versus caesarean section after labour induction

An American chart review study¹⁹⁰ [EL=3] 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). Participants were women who had severe pre-eclampsia and with single live-born babies (24-34 wks' gestation). Maternal age, parity and gestational age at delivery were comparable between the groups.

No differences were found after induction between caesarean section and vaginal delivery in Apgar score < 7 at 5-min and endometritis. Total hospital stay was also no different between the two groups but after excluding three women who had an unusually prolonged hospital stay (> 400 hrs) for unrelated medical conditions (SLE nephritis in two women, and sickle cell disease in the third), total hospital stay became significantly higher in the CS group (130.0 ± 41.1 versus 109.7 ± 44.3, p=0.005).

Evidence statement

When comparing caesarean section without labour with labour induction, a RCT [EL=1-] showed no difference in reported maternal or neonatal complications. However, women allocated to caesarean section stayed for longer periods in the hospital. A retrospective cohort study [EL=2-] showed odds for Apgar score ≤ 3 at 5-min to be significantly lower in the CS group. However, neonatal complications including umbilical artery blood pH ≤ 7.0, respiratory distress, sepsis, intraventricular haemorrhage, seizures and neonatal deaths were statistically insignificant.

When comparing caesarean section with vaginal birth after labour induction, a chart review study [EL=2-] showed no difference between the two groups in reported outcomes (Apgar score < 7 at 5-min and endometritis). Hospital stay, however, was longer in those underwent caesarean section.

GDG interpretation of the evidence

Poor quality small studies seemed to indicate little advantage to caesarean birth although in one study women undergoing caesarean section had longer post-natal 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.

Recommendations

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 criteria⁶:

Level 3	Severe pre-eclampsia and needing ventilation
Level 2	Step-down from level 3 of severe pre-eclampsia with any of the following complications: <ul style="list-style-type: none">- 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	<ul style="list-style-type: none">- Mild or moderate pre-eclampsia- Ongoing conservative antenatal management of severe pre-term hypertension

⁶ Adapted from Intensive Care Society, Standards and Guidelines 2002.

- Step-down treatment after the birth

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).²⁶ 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 (i.e. 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.

Table 11.1 Summary of studies evaluating safety of antihypertensives commonly used during breastfeeding

	Study (first author and year published)	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 1985 ¹⁹¹ USA	3	500-1000 mg/day po	1.02 ± 0.93 µg/ml	0.225 ± 0.199 µg/ml	0.22	In two of the three breastfed babies, plasma levels were undetectable (<0.05 µg/ml) 6hrs after administration of the drug, but in one baby plasma concentration was 0.09 µg/ml 10 hrs 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 µg, or 0.02% of the maternal dose	0.11 ¹⁹²	Nil ^{192,193}	Amount too small to be harmful ¹⁹⁴
	Hauser 1985 ¹⁹⁵ Israel	1	250 mg (1x)	2.5 hrs after dose: 1430 ng/ml	2.5 hrs 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 1985 ¹⁹⁶ Sweden	3	600- 1200 mg/day	228± 178 µg/l	220± 253µg/l	1.5	No consistent pattern in the milk/plasma ratio. 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% ¹⁹²	Nil ^{192,197}	Only small quantities excreted into breast milk ^{192,197}
Propranolol	Taylor 1981 ¹⁹⁸ UK	1	20 mg twice a day	2.25 hrs after last dose: 17 ng/ml 3.25 hr after last dose: 16 ng/ml	2.25 hrs after last dose: 4 ng/ml 3.25 hr after last dose: 11 ng/ml	0.24 0.69	The estimated intake of propranolol by infant was 3 µg daily	0.28% ¹⁹² 0.4% ¹⁹³	Nil ¹⁹²	Monitor for symptoms of beta-blockade ¹⁹⁷ Amount in breast milk low ¹⁹² American Academy of Paediatrics classifies as compatible with breastfeeding ¹⁹⁷ Long term effects on baby not known ¹⁹⁷
	Smith 1983 ¹⁹⁹ Australia	3	40 mg q.i.d	711 ± 49 ng/ml (peak)	429 ± 28 ng/ml (peak)	0.60	None (30 day follow up for baby)			
	Bauer 1979 ²⁰⁰ USA	9	20 mg b.i.d	17 ng/ml (peak)	4 ng/ml (peak)	0.24	No changes in HR			
	Thorley 1983 ²⁰¹ UK	5	40 mg b.i.d	2hrs after dose: 54 ± 14 ng/ml	2hrs after dose: 27 ± 5 ng/ml	2.0	None of the babies showed any clinical signs of beta-blockade			

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Atenolol	White 1984 ²⁰² USA	8	50 mg	0.36 µg/ml	1.3 µg/ml	3.6	Level in infant plasma undetectable (<10 ng/ml); no bradycardia or lethargy	6.6% ¹⁹²	One reported case of bradycardia, cyanosis and hypothermia required hospitalisation ^{192,193,197}	Monitor for symptoms of beta-blockade ¹⁹⁷ Some authors failed to detect atenolol in breast milk ¹⁹² Possible significant transfer to baby and accumulation in premature babies
	Liedholm 1981 ²⁰³ Sweden	1	100 mg	0.62 µg/ml (peak)	1.8 µg/ml (peak)	2.9	-			
	Thorley 1983 ²⁰¹ UK	5	100 mg/day	2hrs after dose: 712 ± 77 ng/ml	2hrs after dose: : 630 ± 121 ng/ml	1.3	None of the babies showed any clinical signs of beta-blockade			
	Kulas 1984 ²⁰⁴ Sweden	4	100 mg (x1)	1658 ± 531 nmol/l	3512 ± 848 nmol/l	2.11	-			
	Schimmel 1989 ²⁰⁵ Canada and Israel	1	50 mg b.i.d		1.5 hr after dose: 469 ng/ml		-			
Metoprolol	Kulas 1984 ²⁰⁴ Sweden	3	100 mg (x1) or 50 mg (x2)	99 ± 37 nmol/l	281 ± 103 nmol/l	2.83	-	1.4% ¹⁹²	Nil ^{192,197}	Maternal plasma levels are small, and so infant dose remains low ¹⁹²
Calcium channel blockers										
Nifedipine	Manninen 1991 ²⁰⁶ Finland	11	10 mg t.i.d	12.04 ± 4.0 ng/ml	4.1 ± 0.8 ng/ml	0.34	-	1.8 ¹⁹²		Amount too small to be harmful, but manufacturer suggests avoid ¹⁹⁴⁻¹⁹⁷
	Penny 1989 ²⁰⁷ UK	1	20 mg	43 ng/ml (peak)	46 ng/ml (peak)	1.07	No babies studied			

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Verapamil	Anderson 1987 ²⁰⁸ Sweden	1	80 mg tds	42.9 ng/ml	25.8 ng/ml	0.60	The ratio between the total dose of verapamil to which the breast-fed 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% ¹⁹²	Nil ^{192:197}	Amount too small to be harmful ¹⁹⁴ , 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
ACE inhibitors										
Enalapril	Redman 1990 ²⁰⁹ UK and Ireland	5	20 mg po (x1)	123± 28 ng/ml (peak)	1.74± 2.41 ng/ml (peak)	0.014	No babies	0.17% ¹⁹²	Nil ¹⁹²	Manufacturer suggests avoid ¹⁹⁴ Can be used in breastfeeding when first-choice agents cannot be used or are ineffective (with monitoring) ¹⁹²
Captopril	Devlin 1981 ²¹⁰ USA	12	100 mg t.i.d (7 doses)	133.4 713.1 ± 140.6 ng/ml (peak)	2.9 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% ¹⁹²	Nil ^{192:197}	Manufacturer suggests avoid ¹⁹⁴ Can be used in breastfeeding when first choice agents cannot be used or are ineffective (with monitoring) ¹⁹²
Vasodilators										
Hydralazine (HDZ)	Liedholm 1982 ²¹¹ Sweden	1	50 mg t.i.d	2 h after a.m. dose: 580 nmol/l (active HDZ) ½ h after midday dose: 1535 nmol/l (active HDZ)	2 h after a.m. dose: 792 nmol/l (active HDZ) ½ h after midday dose: 762 nmol/l (active HDZ)	1.4 0.5	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% ¹⁹²	Nil ^{192:193:197}	Present in milk but not known to be harmful ¹⁹⁴
Thiazide diuretics										
Hydrochlorothiazid ^e	Miller 1982 ²¹² USA	1	50 mg	280 ng/ml (peak)	120 ng/ml (peak)	0.43	No detectable levels (<1 ng/ml); electrolytes normal in baby			

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Chlorothiazide	Werthmann 1972 ²¹³ USA	11	500 mg (x1)	< 1µg/ml	<1 µg/ml	-	No babies studied			
Chlorthalidone	Mulley 1978 ²¹⁴ USA	7	50 mg	6.54± 1.86 µg/ml (peak)	0.37 ± 0.27 µg/ml (peak)	0.06	No babies studied	15.5% ¹⁹³	Nil ¹⁹³	Amount too small to be harmful ¹⁹⁴ American Academy of Paediatrics classifies as compatible with breastfeeding ¹⁹⁷

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; and the thiazide diuretics hydrochlorothiazide, chlorothiazide, and chlorthalidone.

GDG interpretation of the evidence

The GDG is aware of a MHRA newsletter (May 2009 issue of the MHRA Drug Safety Update, available at <http://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 was 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 contact a healthcare professional or emergency service if required (see 'Postnatal care', NICE clinical guideline 37).²⁶

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 recommendations

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 long enough to exclude cumulative effects and they should be large enough to provide reassurance to licensing and drug regulating authorities.

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

12.1 Introduction

The development of new hypertension during pregnancy will have had a 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 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 which investigated the long term risks of cardiovascular events.

One review (Bellamy et al.)¹⁷ [EL=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 > 0.3 g/24 hrs.

A second review (McDonald et al.)²¹⁵ [EL=1++] assessed the long term (> 6 weeks postpartum) cardiovascular sequelae of pre-eclampsia/eclampsia. Both case-control and cohort studies were examined, of which five case-control studies and 10 cohort studies were finally included (total women=2,259,576, 118,990 with 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 CVD and smoking).

The different cardiovascular outcomes studied are listed below and results summarised in Table 12.1.

Risk of future hypertension

Bellamy et al.¹⁷ included 13 studies (21,030 women); 1885 of the 3658 women who had pre-eclampsia developed chronic hypertension in later life. The mean

weighted follow-up was 14.1 years. Women who had pre-eclampsia were at a higher risk of developing hypertension (RR=3.70, 95% CI 2.70 to 5.05) compared with those who did not develop 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 (4 studies; RR= 5.96, 95% CI 3.42 to 10.38) compared with pre-eclampsia in the first pregnancy only (9 studies; RR=3.23, 95% CI 2.32 to 4.52) ($\chi^2 =8.48$, $p =0.004$).

Risk of ischaemic heart disease

Bellamy et al.¹⁷ included eight studies (2,346,997 women); 5097 women of the 121,487 who 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 significant difference between primiparous women with pre-eclampsia and women with pre-eclampsia in any pregnancy. The risk of future fatal ischaemic heart disease events was increased in women after pre-eclampsia (4 studies; RR= 2.60, 95% CI 1.94 to 3.49).

In two studies pre-eclampsia before 37 weeks was associated with nearly an eightfold 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 with severe pre-eclampsia (BP >160/110 mmHg plus proteinuria >0.3 g/24 h or dBp >110 mmHg plus proteinuria >5 g/24 h) were at greater risk of later ischaemic heart disease (RR=2.86, 95% CI 2.25 to 3.65) compared with women with mild pre-eclampsia (RR=1.92, 95% CI 1.65 to 2.24).

McDonald et al.'s²¹⁵ review showed that relative to women with uncomplicated pregnancies, women with a history of pre-eclampsia/eclampsia had an increased risk of subsequent cardiac disease in both the 4 case-control studies (OR= 2.47, 95% CI 1.22 to 5.01) and the 10 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- 2.19), moderate pre-eclampsia (RR 2.99, 95% CI 2.51- 3.58) and severe pre-eclampsia (RR 5.36, 95% CI 3.96-7.27), $p < 0.0001$. Results are homogenous across each of the categories of risk ($I^2=0\%$ for each category)

Risk of cerebrovascular events (stroke)

Bellamy et al.¹⁷ included four studies (1,671,578 women) looking at the risk of strokes in pre-eclamptic women. 907 women out of the 64,551 who had pre-eclampsia developed strokes. The mean weighted follow-up was 10.4 years. The overall risk of fatal and non-fatal stroke after pre-eclampsia was 1.81 (1.45 to 2.27) compared with women who did not develop 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 stroke (2 studies; $RR=2.98$, 95% CI 1.11 to 7.96) was greater than that of non-fatal stroke after pre-eclampsia (2 studies; $RR=1.76$, 1.40 to 2.22).

A diagnosis of pre-eclampsia before 37 weeks was associated with a higher risk of stroke in later life ($RR=5.08$, 95% CI 2.09 to 12.35) compared with a diagnosis of pre-eclampsia after 37 weeks ($RR=0.98$, 0.50 to 1.92).

In the McDonald et al.²¹⁵ review, the single eligible case-control study that examined the risk of cerebrovascular disease reported an increased risk $OR=2.6$ (1.5 to 4.3), in keeping with the pooled estimate in the results from 6 cohort studies ($RR=2.03$, 95% CI 1.54 to 2.67).

Pre-eclampsia and risk of venous thromboembolism

Bellamy et al.¹⁷ included three studies (427,693 women); 470 women out of the 35 772 who 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 did not develop 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) compared with 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.²¹⁵, cohort studies demonstrated that pre-eclamptic/eclamptic women had a non-statistically significant trend toward an increased risk of subsequent peripheral arterial disease (3 cohort studies, $RR=1.87$, 95% CI 0.94 to 3.73)

Risk of cardiovascular mortality

Pooled estimates from 5 cohort studies McDonald et al.²¹⁵ showed that women with a history of pre-eclampsia/eclampsia had a higher relative risk of dying of cardiovascular disease ($RR=2.99$, 95% CI 1.73 to 3.04)

Women with gestational hypertension

Bellamy et al.¹⁷ included two studies, totalling 2106 women, to investigate 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 pregnancy induced hypertension compared with women who did 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 (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 investigated the association between pre-eclampsia/eclampsia and atherosclerosis in later life. Women who had pre-eclampsia were at higher risks of developing cardiovascular events in later life.

Table 12.1 Summary of evidence for risk of long term cardiovascular disease

	Studies in pool estimate	Population	RR (95% CI)	mean follow up (years)	Other factors related
HTN	13 cohort	PE	3.70 (2.70 to 5.05)	14.1	- Pre-eclampsia in any > 1 st pregnancy

IHD	8 cohorts	PE	2.16, 1.86 to 2.52	11.7	- Pre-eclampsia before 37 > after 37 wks - Severe > moderate > mild pre-eclampsia
	10 cohorts	PE/E	2.33, 1.95-2.78		
	4 case-controls	PE/E	OR= 2.47, 1.22-5.01		
Stroke	4 cohorts	PE	1.81, 1.45 -2.27	10.4	- Risk of fatal stroke > non-fatal stroke - Pre-eclampsia before 37 > after 37 wks
	6 cohorts	PE/E	2.03, 1.54 to 2.67		
	1 case-control	PE/E	OR=2.6, 1.5 to 4.3		
VTE	3 cohorts	PE	1.79, 1.37- 2.33)	4.7 yrs	- Severe > mild pre-eclampsia
PAD	3 cohorts	PE/E	1.87, 0.94 to 3.73		
Mortality of CVD	5 cohorts	PE/E	2.99, 1.73 to 3.04		

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.

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.

Recommendations

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 recommendations

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 [EL=2++]²¹⁶ looked at the association between pre-eclampsia in one or more pregnancies and the subsequent risk of end-stage renal disease (ESRD). 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 (\pm SD) duration of follow-up after the first, second and third pregnancies were 26.5 \pm 7.5, 22.8 \pm 0.8 and 18.7 \pm 8.2 years, respectively. The mean ages of the mother at the first, second and third deliveries were 23.5 \pm 4.3, 26.9 \pm 4.3 and 30.2 \pm 4.3 years, respectively.

ESRD developed in 477 of 570,433 women a mean (\pm SD) of 17 \pm 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 ESRD of 4.7 (95% confidence interval [CI], 3.6 to 6.1) (Table 11.2). Among women who had been pregnant two or more times, pre-eclampsia during the first pregnancy was associated with a relative risk of ESRD 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 ESRD of 6.3 (95% CI, 4.1 to 9.9), and preeclampsia during two or three pregnancies was associated with a relative risk of 15.5 (95% CI, 7.8 to 30.8).

Separate analyses setting the baseline at 10 years after the pregnancy of interest confirmed a significant association between pre-eclampsia and ESRD. These analyses showed that after one pregnancy with pre-eclampsia, the relative risk of ESRD was 4.1 (95% CI, 3.1 to 5.5); after two pregnancies, the relative risk of ESRD 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 ESRD varied, depending on whether pre-eclampsia occurred during the first pregnancy (relative risk, 2.6; 95% CI, 1.1 to 5.9), the second pregnancy (relative risk, 7.3; 95% CI, 3.0 to 18.1), or the third pregnancy (relative risk, 14.3; 95% CI, 8.2 to 24.7). The associations between pre-eclampsia and ESRD remained 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 big retrospective cohort study [EL=2++] showed that end-stage kidney disease developed in 477 of 570,433 women a mean (\pm SD) of 17 \pm 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 ESRD 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 ESRD 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, preeclampsia during one pregnancy was associated with a relative risk of ESRD 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 risk of end-stage renal disease

Variable	Total No. of women	No. with ESRD	No./100,000 Person-Yr (95% CI)**	Adjusted Relative Risk (95% CI)†
<i>After first pregnancy (all women)</i>				
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)
<i>After second pregnancy (women with ≥ 2 pregnancies)</i>				
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)
<i>After three pregnancies (women with ≥ 2 pregnancies)</i>				
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)*
Pre-eclampsia in second pregnancy only	1,875	5	16.2 (5.1- 33.4)	7.3 (3.0- 18.1)*
Pre-eclampsia in third pregnancy only	2,922	15	30.6 (17.1- 48.1)	14.3(8.2- 24.7)*
Pre-eclampsia in ≥ 2 pregnancies	1,741	9	32.9 (14.9- 57.9)	10.9 (5.0- 23.8)

GDG interpretation of the evidence

The risk of end stage kidney disease is increased in women who have had previous pre-eclampsia though 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.

Recommendations

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 end-stage 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

A health technology assessment (HTA, 2006)²¹⁷ [EL=1++] looked at screening for thrombophilia in high risk pregnancies. It assessed the risk of clinical complications, including pre-eclampsia, associated with thrombophilia.

All prospective and retrospective studies of venous thromboembolism (VTE) events and thrombophilia in women taking oral oestrogen preparations and patients undergoing major orthopaedic surgery and studies of VTE 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. ORs 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 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 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 (FVL) homozygosity was not found as a significant predictor of pre-eclampsia (OR=1.87, 95% CI 0.44 to 7.88); heterozygotes were at a 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 significantly associated with pre-eclampsia. Similarly, neither lupus anticoagulants nor acquired APCR was found to put women at significantly higher risk of developing pre-eclampsia.

In total, women having any of the thrombophilias are at a significantly higher risk of developing pre-eclampsia than those who do not have thrombophilias (688/1190 versus 6222/13985: 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 Evidence summary of the risks of pre-eclampsia and thrombophilia

Thrombophilia	Odds Ratio (95% CI)
Hyperhomocysteinaemia	OR=3.49 (1.21 to 10.11)
Prothrombin heterozygous	OR=2.73 (1.65 to 4.51)
Anticardiolipin antibodies	OR=2.54 (1.52 to 4.23)
FVL heterozygotes	OR=2.34 (1.56 to 3.51)
MTHFR homozygous	OR=1.32 (1.05 to 1.66)

The following thrombophilias were not found to be significantly associated with pre-eclampsia:

- FVL homozygous
- antithrombin III deficiency
- protein C deficiency
- protein S deficiency
- lupus anticoagulants
- acquired APCR.

In total, women having some of the thrombophilias are at a significantly higher risk of developing pre-eclampsia than those who do not have thrombophilias (688/1190 versus 6222/13985: 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 thrombo-embolism is outside the scope of this guideline.

Recommendations

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 studies²¹⁸⁻²²² [EL=2+] investigated recurrence of hypertensive disorders of pregnancy in women who had gestational hypertension in index pregnancy. The studies were conducted in Iceland, Scotland, the USA and Australia (n=2). In two studies,^{218;220} index pregnancy was the first pregnancy and recurrence was investigated in the second pregnancy. In the other three studies,^{219;221;222} index pregnancy was not always first pregnancy and subsequent pregnancies were not always consecutive but only one subsequent pregnancy was included.

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 gestational hypertension

Study	No. of participants	Gestational hypertension % (n)	Pre-eclampsia % (n)
Hjartardottir 2006 Iceland ²¹⁸	n=511	47% (240)	7% (36)
Brown 2007 Australia ²¹⁹	n= 367	26% (95)	3% (11)
Hargood 1991 Australia ²²¹	n= 121	44% (53)	2% (2)
Campbell 1985 Scotland ²²⁰	n= 1339	29% (388)	2% (27)
Zhang 2001 USA ²²²	n= 237	16% (38)	3% (7)

Previous pregnancy with pre-eclampsia

Nine retrospective cohort studies^{10 218-225} [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 (n=2), Australia (n=2), Norway, Denmark and Sweden. In six studies,^{10 218;220;223-225} the index pregnancy was the first pregnancy and recurrence was investigated in the next (second) pregnancy. In the other three studies,^{219;221;222} 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%.

One large Swedish retrospective cohort study¹⁰ [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 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. Similarly, 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 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 two years and 2.2% if they became pregnant more than eight years after their first pregnancy; the corresponding risks were 13.1% and 15.8% for women with pre-eclampsia in their first pregnancy.

Table 12.5. Summary of studies that presented the risk of recurrence of pregnancy-related hypertension in women with pre-eclampsia

Study	No. of participants	Gestational hypertension	Pre-eclampsia
Hjartardottir 2006 Iceland ²¹⁸	n= 151	34% (51)	13% (20)
Brown 2007Australia ²¹⁹	n= 239	13% (31)	9% (22)
Hargood 1991Australia ²²¹	n= 19	53% (10)	5% (1)
Hernandez-Diaz 2009 Sweden ¹⁰	N=19,540	-	14.7% (2,871)
Trogstad 2004 Norway ²²⁴ : Singleton	n= 19,960	-	14% (2,749)
Trogstad 2004 Norway ²²⁴ : Twin	n= 325	-	7% (23)
Campbell 1985 (Scotland) ²²⁰	n= 279	30% (84)	7.5% (21)
Basso 2001 Denmark ²²³	n= 8,401	-	16% (1,344)
Mostello 2008 USA ²²⁵	n= 6157	-	15% (924)
Zhang 2001* USA ²²²	n= 34	32% (11)	0% (0)

Effect of severity

Previous pregnancy with severe pre-eclampsia

One retrospective cohort study²²⁶ [EL 2+] was conducted in the USA and investigated the recurrence of hypertensive disorders of pregnancy in 108 women with severe pre-eclampsia in index pregnancy (gestational age 18-27 weeks). These women had 169 subsequent pregnancies (follow up: average 5.4 yrs, range: 2-12 years). The study showed that 65% (110/169) of subsequent pregnancies were complicated with pre-eclampsia, as shown in Table 12.6.

Two retrospective cohort studies used birth before 34 weeks gestation as a surrogate for severe disease.^{10 227} The first study was a large Swedish retrospective cohort study¹⁰ [EL=2+] investigated the recurrence risk of pre-eclampsia. 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 study²²⁷ [EL=2+] was conducted in the Netherlands and investigated the risk of recurrence of pre-eclampsia in subsequent pregnancy after early-onset pre-eclampsia (gestational age <34 weeks) in first pregnancy. 120 primiparous women were included (follow-up: average 6.3 years). 27 women (22.5%) developed gestational hypertension in the next pregnancy while 30 others (25.0%) developed pre-eclampsia, as shown in Table 12.6.

The risk of recurrence of pre-eclampsia across the three cohort studies^{10;226;227} 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 studies²²⁸⁻²³⁰ [EL=2+] investigated the risk of recurrence of hypertensive disorders of pregnancy in subsequent pregnancies in women who had HELLP syndrome in their index pregnancy. All studies were conducted in the USA and overall 435 women were included.

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 occurred before 28 weeks.²³⁰ One study reported results on developing gestational hypertension in subsequent pregnancies and showed a risk of 9% (19/212).

Previous pregnancy with eclampsia

Two cohort studies^{231,232} [EL 2+] investigated the risk of recurrence of hypertensive disorders of pregnancy in subsequent pregnancies in women who had eclampsia in their index pregnancy.

The first study was a prospective cohort conducted in Nigeria which included 64 women who had eclampsia during their index pregnancy. These women were followed up in their next pregnancy. Ten women (15.6%) had a recurrence of eclampsia in next pregnancy, as shown in Table 12.5.

The second study was a retrospective cohort conducted in the USA and included 182 women who had eclampsia in their index pregnancy. These women had 366 subsequent pregnancies (follow up: average 7.2 years, range 3-13 years). 159 of those 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 1.9% (7/366), while the risk of pre-eclampsia was 22% (80/366), 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 HELLP syndrome, eclampsia, severe pre-eclampsia or pre-eclampsia that developed before 34 weeks

Index pregnancy	Study	No. of participants	Gestational hypertension	Pre-eclampsia	Eclampsia	HELLP
HELLP	Sullivan 1994 USA ²²⁸	n=161	-	43% (n= 69)	-	19% (n= 31)
	Sibai 1995 USA ²²⁹	n= 212	9% (n=19)	24% (n= 51)	-	3% (n= 6)
	Chames 2003 USA ²³⁰ Delivery < 28 wks	n= 62	-	55% (n= 34)	-	6% (n= 4)
Eclampsia	Adelusi 1986 Nigeria: ²³¹	n= 64	-	-	16% (n= 10)	-
	Sibai 1992 USA ²³²	n= 366	-	22% (n=80)	2%(n= 7)	-
Severe pre-eclampsia	Sibai 1991 USA ²²⁶ Severe pre-eclampsia	n= 169	-	65% (n=110)	-	-
	Rijn 2006 Netherlands ²²⁷ Delivery < 34 weeks	n= 120	22.5% (n=27)	25% (n=30)	-	-
	Hernandez-Diaz 2009 Sweden ¹⁰ Delivery < 34 weeks	n=1,754	-	29% (n=509)	-	-

Effect of gestational age at presentation

Previous pregnancy with gestational hypertension

One retrospective cohort study²¹⁸ [EL=2+] was conducted in Iceland and investigated the risk of recurrence of hypertensive disorders of pregnancies in second pregnancies in 411 women who had gestational hypertension in their first pregnancy. In comparison with late onset gestational hypertension, early onset gestational hypertension (≤ 34 gestational weeks) 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 study²²⁰ [EL=2+] was conducted in Scotland and investigated the risk of recurrence of hypertensive disorders of pregnancy in the second pregnancy in 1,270 women who 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% (0/28) to 2.1% (26/1242) 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 21.4% (6/28) to 29.1% (361/1242).

Previous pregnancy with pre-eclampsia

One retrospective cohort study²²⁰ [EL=2+] conducted in Scotland investigated the risk of recurrence of hypertensive disorders of pregnancy in second pregnancy in 264 women who had pre-eclampsia in their first pregnancy. Comparison of women by the gestational age at which they developed gestational hypertension in the index pregnancy showed that the risk of pre-eclampsia in the second pregnancy decreased from 13.0% (3/23) to 6.8% (16/234) if the first pregnancy went to term (28-36 wks, versus 37-45 wks), and the risk of gestational hypertension decreased from 39.1% (9/23) to 29.5% (69/234)

One retrospective cohort study²²⁵ [EL 2+] was conducted in the USA and investigated recurrence of pre-eclampsia in second pregnancy based on gestational age at delivery for the first pregnancy complicated by pre-eclampsia. 6,157 women with pre-eclampsia in first pregnancies were included. The risk of recurrent pre-eclampsia was about 12% for those who previously delivered at term and increased to nearly 40% for those whose prior delivery occurred at less than 28 weeks.

The retrospective cohort study²¹⁸ [EL=2+] conducted in Iceland also investigated the risk of recurrence of hypertensive disorders of pregnancies in second pregnancies in 151 women who had pre-eclampsia in their first pregnancy. In comparison with late onset pre-eclampsia, early onset pre-eclampsia (≤ 34 gestational weeks) 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

One retrospective cohort study²²⁸ [EL=2+] was conducted in the USA and investigated recurrence in subsequent pregnancies in women who had HELLP syndrome in 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. Eleven of these 18 (61%) were subsequently delivered at ≤ 32 weeks. 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

One retrospective cohort study²³² [EL=2+] was conducted in the USA and 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, 334 subsequent pregnancies). The women who had eclampsia before 37 weeks had significantly higher incidences of pre-eclampsia in subsequent pregnancies as compared with women who had eclampsia at ≥ 37 weeks (43% ≤ 30 weeks; 32% 31-36 weeks, 8% 37-41 weeks, $p < 0.001$). As for recurrence of eclampsia, no significant difference was detected (1.8% ≤ 30 wks; 1.7% 31-36 wks, 2.4% 37-41 weeks, p -value=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 presents before 34 weeks,^{10 228 229 230 231 232 226 227} ranged from 22% to 65%, as shown in Table 12.5.

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% to 47% and a recurrence risk for pre-eclampsia of 2% to 7%.

One retrospective cohort study [EL 2+] (n=411) showed no differences between late and early onset of gestational hypertension (≤ 34 weeks gestation) 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 21.4% 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 eight retrospective cohort studies [EL=2+] showed a recurrence risk for gestational hypertension of 13% to 53% and a recurrence risk for pre-eclampsia of 0% to 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 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 25.0% risk of developing pre-eclampsia in next pregnancy.

Using HELLP syndrome as a surrogate for severity, evidence from three retrospective cohort studies [EL=2+] reported recurrence risks of 3% to 19% for HELLP syndrome in a subsequent pregnancy, and 24% to 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% to 16% for developing eclampsia in a subsequent pregnancy.

Examining the effect of gestational age at which pre-eclampsia developed, one retrospective cohort study [EL=2+] (n=411) showed no statistically significant differences between late and early onset of pre-eclampsia (≤ 34 weeks gestation) 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) decreased from 13.0% to 6.8%, and the risk of developing gestational hypertension decreased from 39.1% to 29.5%. A large retrospective cohort study [EL=2+] (n=6,157) showed that the recurrence risk of pre-eclampsia was about 12% for those who previously delivered at term and increased to nearly 40% for those whose previous delivery occurred at less than 28 weeks.

Another complex retrospective cohort study showed that women who had eclampsia before 37 weeks had significantly higher incidence of pre-eclampsia in a subsequent pregnancy compared with women who had eclampsia at ≥ 37 weeks (43% ≤ 30 weeks; 32% 31-36 weeks, 8% 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; and 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% to 65%) where the index pregnancy is complicated by severe disease (variously defined) or where disease of any severity presents 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 occurs at less than 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 ranges from zero (0%) 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 Inter-pregnancy interval and recurrence of hypertensive disorders of pregnancy

Clinical effectiveness

One cohort study was identified [EL=2+] ²²³ undertaken in Denmark between 1980 and 1994 to assess the risk of recurrent pre-eclampsia in relation to inter-pregnancy intervals and change of partner. There were 8401 women with a diagnosis of pre-eclampsia in their first pregnancy who had a subsequent pregnancy and 26596 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. Inter-pregnancy 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 inter-pregnancy intervals but those who had not had pre-eclampsia in their first pregnancy had increasing risk with increased inter-pregnancy interval. The least risk in both groups was with an inter-pregnancy 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 inter-pregnancy 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.

Recommendations

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

One retrospective cohort study²²⁵ [EL=2+] was conducted in the USA and investigated recurrence of pre-eclampsia in second pregnancy and investigated the effect of body mass index of the women between the pregnancies. 6,157 women with pre-eclampsia in first pregnancies were included. The overall risk of recurrence in the 2nd pregnancy was 14.7%.

The study shows pre-eclampsia risks increasing linearly with increasing BMI for all gestational age categories, as summarised in Table 11.7.

Table 12.7 Pre-eclampsia recurrence risk by BMI and gestational age (GA)

T	Prior pre-eclampsia		
	GA 20-32	GA 33-36	GA 37-47
< 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 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 [cross-refer to healthy range in NICE obesity guidance] will reduce the recurrence risk and it is a modifiable factor.

Recommendations

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

AC:	albumin creatinine ratio
ACE :	angiotensin-converting enzyme
ACOG :	American College of Obstetricians and Gynecologists
ACR :	albumin creatinine ratio
ALT :	alanine aminotransferase
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
BP:	blood pressure
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
CVD :	cardiovascular disease
dl:	decilitre
EL:	evidence level
ESRD:	end stage renal disease
FDA:	Food and Drug Administration
FHR:	fetal heart rate
FVL:	Factor V Leiden
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

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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 entero-colitis
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 values
NST:	non-stress test
OR:	odds ratio
PDI:	Psychomotor Development Index
PET:	pre-eclampsia
PI:	pulsatility index
PPV:	positive predictive value
QADAS:	quality assessment of studies of diagnostic accuracy in systematic review
QALY:	quality adjusted life year
RCT:	randomised controlled trial
RI:	resistance index
RPE:	rating of perceived exertio
RR:	relative risk
SCBU:	special care baby unit
SD:	standard deviation
SGA:	small-for-gestational age
SLE:	systemic lupus erythematosis
SPC:	summary of product characteristics
UK:	United Kingdom
USA:	United States of America
VTE:	venous thromboembolism
WMD:	weighted mean difference

13.3 Glossary

Abruption/Abruptio placentae	Separation of the placenta before the baby is born
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 aminotransferase (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 dipstick test/ reading	A method of testing for protein in the urine using a machine
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

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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

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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

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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 (FHR)	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 < 20ml 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	See abruptio placentae
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 >500mls
Pre-eclampsia	New hypertension after 20 weeks of pregnancy

	with significant proteinuria (more than 300 mg in a 24-hour urine collection).
Prematurity	Relates to a fetus/baby born before 37 weeks gestation
Pre-term 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	See definitions in introduction
Severe pre-eclampsia	See definition in introduction
Single Deepest Vertical Pool (SVDP)	A measure of amniotic fluid where the largest individual pool of fluid is recorded > 300mg/24 hours
Significant proteinuria	
Systemic lupus erythematosus	A chronic inflammatory condition that can involve joints, kidneys, heart lungs and brain.
Small for gestational age	Usually defined as being below a certain birth weight 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
Thrombocytopenia	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 well-being; not merely the absence of disease.
Incremental cost-effectiveness	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

ratio (ICER)

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 Each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study.

(univariate analysis):
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.'

Hypertension in pregnancy Page 7 of 7

Appendix B

Declarations of interest

This appendix includes all interests declared on or before 14 December 2009.

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 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

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No interests declared

Khalid Ashfaq

No interests declared

Ella Fields

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

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

Appendix C

Registered stakeholder organisations

[To be updated at publication - please see NICE website for current list]

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

Cytec 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

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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

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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?

Appendix E - L

These appendices are presented as separate files for consultation

Appendix M

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 birth weight, 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 birth weight compared to those exposed to atenolol (3280g versus 2750g).

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 – 100-300mg 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 to 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, birth weight 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 100mg 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 160mg 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 1mg IV propranolol just before C-section.

Fetal bradycardia has been reported in women having 1mg/minute propranolol for 4 minutes for dysfunctional labour.

An increase in perinatal mortality has been described in a small study when compared to 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 birth weight 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, birth weight, 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 5mg/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 2mg/kg then 200mcg/kg/min - No long lasting effects were seen on this infant after birth.

Another case in a woman at 38 weeks gestation received 0.5mg/kg bolus followed by a continuous infusion of 50mcg/kg/min. FHR before drug was 150-160bpm and increased to 170-175bpm 20 minutes after, at 24 minutes FHR 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 25mcg/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 where 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 β -blockade were seen in the foetuses or neonates.

There are several conflicting studies that either do or do not show IUGR and low birth weight.

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 (20mg/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 β -blockade; 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 to 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 to methyldopa in pregnancy neonates are significantly larger (3051g versus 2654g), 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 birth weights 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, birth weight, 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 (60mg QDS) use in the 1st month of pregnancy (with Isosorbide dinitrate 20mg 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 to 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 to 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 2.5mg BD for 4 days then 5mg 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 5mg OD for 4 days then 5mg BD in the 3rd trimester showed no adverse effects in the newborn except one who's birth weight 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 to 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

Bendrofluzide (Limited human data) (Cm*) (D – for gestational hypertension)

See chlorothiazide

A study reported 1011 women who received 5mg bendrofluzide 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 chlorthalidone (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

Cyclopenthiiazide

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 toxemia 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.

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There are conflicting reports of alopecia, hypertrichosis and decreased ossification of the wrist in neonates exposed to diazoxide 19-69 days before delivery.

Appendix N

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						
Bendrofluzide					Amount too small to be harmful ¹⁹⁴ Large doses may suppress lactation ^{192,194,197} American academy of paediatrics classifies as compatible with breastfeeding ¹⁹⁷	
Chlortalidone	0.062	15.5% ¹⁹³	Nil ¹⁹³		Amount too small to be harmful ¹⁹⁴ Long half life and may accumulate in milk ¹⁹³ Highly plasma protein bound ¹⁹³ Large doses may suppress lactation ^{192,194}	
Cyclopenthaizide					Amount too small to be harmful ¹⁹⁴ Large doses may suppress lactation ¹⁹⁴	
Indapamide				Milk supply ¹⁹² Volume depletion ¹⁹²	No reports of exposure via breast milk ¹⁹² Manufacturer suggests avoid ¹⁹⁴ May suppress lactation ¹⁹⁷	
Metolazone					Amount too small to be harmful ¹⁹⁴ Large doses may suppress lactation ¹⁹⁴	
Loop diuretics						
Furosemide	0.5-0.82		Nil ¹⁹²		Amount too small to be harmful ¹⁹⁴ Very unlikely that quantity transmitted in breast milk would produce effects in a nursing infant (relatively high doses used therapeutically in children) ¹⁹² Large doses may suppress lactation ^{192,194}	
Toraseamide					No reports of exposure through breast milk ¹⁹² High plasma protein binding ¹⁹² May reduce milk supply ¹⁹²	
Other diuretics						
Amiloride					No human exposure via breast milk reported ¹⁹⁷ Passage into milk is expected ¹⁹⁷	

Beta-blockers						
Propranolol	0.2-1.54 0.33-1.65 (average 0.5) ¹⁹²	0.28% ¹⁹² 0.4% ¹⁹³	Nil ¹⁹²	Monitor for symptoms of beta-blockade ¹⁹⁷	Amount in breast milk low ¹⁹² American academy of paediatrics classifies as compatible with breastfeeding ¹⁹⁷ Long term effects on infant not known ¹⁹⁷	Circulatory problems and Hypoglycaemia reported in breastfeeding infants ¹⁹³ Possible toxicity due to beta-blockade but amount of most beta-blockers present in milk too small to affect infant ¹⁹⁴
Acebutolol	1.9-9.2 (active metabolite 2.3-24.7) ¹⁹² 252 1.9-9.8 (1.5-24.7 active metabolite) ¹⁹⁷	3.6% ¹⁹²	Symptoms of beta-blockade have been observed (Hypotension, bradycardia, tachypnoea and drowsiness) ^{192;193;197}	Symptoms of beta-blockade ¹⁹⁷	Low protein binding and primary excretion via kidneys ¹⁹³ Possible significant transfer to baby and accumulation in premature infants ^{193;194}	
Atenolol	1.5-6.8 ¹⁹² 1.1-6.8 ¹⁹³	6.6% ¹⁹²	One reported case of bradycardia, cyanosis and hypothermia required hospitalisation ^{192;193;197}	Symptoms of beta-blockade ¹⁹⁷	Low protein binding and primary excretion via kidneys ¹⁹³ Some authors have failed to detect atenolol in breast milk ¹⁹² Possible significant transfer to baby and accumulation in premature infants ^{193;194;197}	
Bisoprolol			Nil ¹⁹²	Hypotension, bradycardia, other symptoms of beta-blockade ¹⁹⁷	No reports of use in lactating mothers ¹⁹⁷	
Carvedilol				Hypotension, bradycardia, other symptoms of beta-blockade ¹⁹⁷	No human data available ^{192;197} Highly lipid soluble and low molecular weight – transfer into milk expected ¹⁹²	
Labetalol	0.2-1.5 ¹⁹³ 0.8-2.6 ¹⁹²	0.57% ¹⁹²	Nil ^{192;197}	hypotension and apnoea ¹⁹² Hypotension, bradycardia, other symptoms of beta-blockade ¹⁹⁷	Only small quantities excreted into breast milk ^{192;197}	
Metoprolol	3-3.72 ¹⁹²	1.4% ¹⁹²	Nil ^{192;197}	Hypotension, weakness, bradycardia and other symptoms of beta-blockade ^{192;197}	Concentrated in breast milk – with milk levels approx ¹⁹² times that of maternal plasma ¹⁹⁷ Maternal plasma levels are small and so infant dose remains low ¹⁹²	
Nadolol	4.6 ¹⁹²	4.6% ¹⁹²		Symptoms of beta-blockade ¹⁹⁷	Long half life ¹⁹² Secreted into breast milk in moderately high amounts, possible significant transfer to baby and accumulation in premature infants ^{192;194} Milk levels 4.6 times greater than maternal plasma ¹⁹⁷	
Oxprenolol	0.14-0.45 ¹⁹⁷		Nil ¹⁹⁷	Bradycardia and other symptoms of beta-blockade ¹⁹⁷	Excreted into breast milk, amounts likely insignificant for the infant ¹⁹⁷	
Pindolol				Bradycardia and other symptoms of beta-blockade ¹⁹⁷	Manufacturer states present in breast milk ¹⁹⁷ No reports of exposure though breast milk reported ¹⁹⁷	
Timolol	0.8-0.83 ¹⁹⁷	1.1% ¹⁹²	Nil ^{192;197}	Hypotension, weakness, hypoglycaemia, sedation and depression Bradycardia and other symptoms of beta-blockade ¹⁹⁷	Levels in breast milk unlikely to be significant ¹⁹²	
Alpha blockers						
Doxazocin					No reports of use in human lactation ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Prazocin					No reports of use in human lactation ¹⁹⁷	

					Manufacturer reports small amounts in breast milk ¹⁹⁷ Amount probably too small to be harmful ¹⁹⁴ May reduce milk production ¹⁹²	
Terazosin					No reports of use in human lactation ¹⁹⁷ Transfer into milk is expected ¹⁹⁷	
ACE inhibitors						
Captopril	0.032 0.012 ^{192:197}	0.02% ¹⁹²	Nil ^{192:197}	Hypotension ¹⁹²	Manufacturer suggests avoid ¹⁹⁴ Excreted into breast milk in low concentrations ¹⁹⁷ Can be used in breastfeeding ¹⁹⁷ when first choice agents cannot be used or are ineffective (with monitoring) ¹⁹²	
Enalapril	0-0.14 (0.021- 0.031 metabolite) ¹⁹⁷ 0.013-0.025 ¹⁹²	0.17% ¹⁹²	Nil ¹⁹²	Hypotension ¹⁹²	Amount probably too small to be harmful ^{194:197} Can be used in breastfeeding when first choice agents cannot be used or are ineffective (with monitoring) ¹⁹² Caution in pre-term infants – risk of renal toxicity ¹⁹²	
Fosinopril			Nil ¹⁹²		Barely detectable levels present in breast milk (no values reported) ¹⁹² Manufacturer suggests avoid ¹⁹⁴	
Imidapril					Manufacturer suggests avoid ¹⁹⁴	
Lisinopril					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Moexipril					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Perindopril					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected (including its active metabolite) ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Quinapril	0.12 ^{192:197}	1.63	Nil ¹⁹²		Present in breast milk ¹⁹⁷ Amounts available in breast milk clinically insignificant ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Ramipril	0.25% ¹⁹²		Nil ¹⁹²	Hypotension ¹⁹²	No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Trandolapril					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Angiotensin II receptor blockers						
Candesartan					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Eprosartan					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	

Irbesartan					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Losartan					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Olmesartan					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Telmisartan					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Valsartan					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷ Manufacturer suggests avoid ¹⁹⁴	
Calcium channel blockers						
Amlodipine.			Nil ¹⁹²		No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ^{192:197} Manufacturer suggests avoid ¹⁹⁴	
Diltiazem	0.2-0.92 13	0.8% ¹⁹²		Hypotension, bradycardia ¹⁹²	Significant amount present in milk – no evidence of harm but avoid unless no safer alternative ¹⁹³ Present in breast milk at similar levels to that of maternal plasma ¹⁹⁷	
Felodipine					No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷	
Isradipine			Nil ¹⁹²	Hypotension, fatigue, bradycardia and apnoea ¹⁹²	Manufacturer suggests avoid ¹⁹⁴ No reports of use during human lactation ¹⁹⁷ Excretion into human breast milk should be expected ¹⁹⁷	
Lercanidipine					Manufacturer suggests avoid ¹⁹⁴	
Nicardipine	0.08-0.75 ¹⁹²	0.07% ¹⁹²			No reports of use during human lactation ¹⁹⁷ Manufacturer suggests avoid ^{194:197}	
Nifedipine	13	1.83			Amount too small to be harmful (but manufacturer suggests avoid) ^{194:197}	
Verapamil	0.2-0.92 0.94 ¹⁹²	0.15-0.98% ¹⁹²	Nil ^{192:197}	Hypotension, bradycardia, weakness ¹⁹²	Amount too small to be harmful ¹⁹⁴	
Other antihypertensives						
Clonidine	1.54 23	7.5% ¹⁹²	Nil ^{192:193:197}	Hypotension ¹⁹²	May reduce milk production ¹⁹² Manufacturer suggests avoid ¹⁹⁴	
Methylidopa	0.2-0.52 0.19-0.34 ¹⁹²	0.11 ¹⁹²	Nil ^{192:193}		Amount too small to be harmful ¹⁹⁴	
Moxonidine	1-2 ¹⁹³				Manufacturer suggests avoid ¹⁹⁴	
Hydralazine	0.49-1.36 ¹⁹² 0.52 1.44	1.2% ¹⁹²	Nil ^{192:193:197}	Hypotension, sedation, weakness ¹⁹²	Present in milk but not known to be harmful ^{194:197}	

