Hypertension in pregnancy
the management of hypertensive disorders during pregnancy

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

Commissioned by the National Institute for Health and Clinical Excellence

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Acknowledgements

To be completed for publication.
1  **Summary of recommendations and care pathway**

### 1.1 Key priorities for implementation

**Reducing the risk of hypertensive disorders in pregnancy**

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

- hypertensive disease during a previous pregnancy
- chronic renal 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**

Advise women of childbearing age 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 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.

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1 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.
**Management of pregnancy after a diagnosis of new-onset hypertension without significant proteinuria (gestational hypertension)**

Manage gestational hypertension as described in the table below:

<table>
<thead>
<tr>
<th>Degree of Hypertension</th>
<th>Mild Hypertension (&lt;149/99 mmHg)</th>
<th>Moderate Hypertension (150/100 to 159/109 mmHg)</th>
<th>Severe Hypertension (160/110 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admit to hospital</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Treat</strong></td>
<td>No</td>
<td>Yes - with oral labetalol&lt;sup&gt;2&lt;/sup&gt; to keep:</td>
<td>Yes - with oral labetalol&lt;sup&gt;2&lt;/sup&gt; to keep:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• diastolic blood pressure less than 100 mm Hg but more than 80 mm Hg</td>
<td>• diastolic blood pressure less than 100 mm Hg but more than 80 mm Hg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• systolic blood pressure less than 150 mm Hg</td>
<td>• systolic blood pressure less than 150 mm Hg</td>
</tr>
<tr>
<td><strong>Measure blood pressure</strong></td>
<td>Yes routinely not more than once a week</td>
<td>Yes at least twice a week</td>
<td>Yes at least four times a day</td>
</tr>
<tr>
<td><strong>Test for proteinuria</strong></td>
<td>Yes at each visit using automated dipsticks</td>
<td>Yes at each visit using automated dipsticks</td>
<td>Yes daily using automated dipsticks</td>
</tr>
<tr>
<td><strong>Blood tests</strong></td>
<td>No (none in addition to those for routine antenatal care)</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• test urea electrolytes and request a full blood count, platelets, serum creatinine, transaminases, bilirubin</td>
<td>• test at presentation: full blood count, platelets, serum creatinine, transaminases, bilirubin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• do not carry out further blood tests if no proteinuria at subsequent visits.</td>
<td>• monitor weekly: full blood count, platelets, serum creatinine, transaminases, bilirubin</td>
</tr>
</tbody>
</table>

Offer birth to women with gestational hypertension whose diastolic blood pressure is greater than 95 mmHg with or without antihypertensive treatment after 37+0 weeks.

**Management of pregnancy with pre-eclampsia**

Manage pre-eclampsia as described in the table below:

<table>
<thead>
<tr>
<th>Degree of Hypertension</th>
<th>Mild Hypertension (&lt;149/99 mmHg)</th>
<th>Moderate Hypertension (150/100 to 159/109 mmHg)</th>
<th>Severe Hypertension (160/110 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Admit to hospital</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Treat</strong></td>
<td>No (none in addition to routine antenatal care)</td>
<td>Yes with oral labetalol&lt;sup&gt;2&lt;/sup&gt; to keep:</td>
<td>Yes with oral labetalol&lt;sup&gt;2&lt;/sup&gt; to keep:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• diastolic blood pressure less than 100 mm Hg but more than 80 mm Hg</td>
<td>• diastolic blood pressure less than 100 mm Hg but more than 80 mm Hg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• systolic blood pressure less than 150 mm Hg</td>
<td>• systolic blood pressure less than 150 mm Hg</td>
</tr>
<tr>
<td><strong>Measure blood</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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<sup>2</sup> Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.
Consultant obstetric staff should advise and document the biochemical, haematological and clinical thresholds (maternal and fetal) for birth in women with pre-eclampsia before 34 weeks.

In women who have had pre-eclampsia perform medical review at the postnatal visit (6-8 weeks after the birth).

**Advice at discharge from maternity care**

Inform women that if they had pre-eclampsia in their first pregnancy their risk of developing:

- gestational hypertension in their next pregnancy is 1 in 4 (26%)
- pre-eclampsia in their next pregnancy is around 1 in 7 (14.5%)
- pre-eclampsia in their next pregnancy is 1 in 4 (25%) if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks and 1 in 2 (55%) if it led to birth before 28-30 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 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.

In addition, 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.
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* 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 renal disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

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

- first pregnancy
- age more than 40 years
- body mass index (BMI) more than 35 at first visit
- family history of pre-eclampsia
- multiple pregnancy.

Other pharmaceutical agents

Do not use the following for the prevention of hypertensive disorders during pregnancy:

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

Nutritional supplements

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

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

Diet

Do not advise salt restriction during pregnancy 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.

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 2006).
clinical guideline 34), unless it specifically differs from recommendations in this
guideline.

Pre-pregnancy advice
Advising women of childbearing age 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 alternative antihypertensive treatment with their healthcare
  professional if they are planning pregnancy.

Review antihypertensive treatments for women taking ACE inhibitors or ARBs when
they become pregnant (preferably within 2 working days of notification of
pregnancy) and discuss alternatives.
Advising women of childbearing age 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 alternative antihypertensive treatment with their healthcare
  professional if they are planning pregnancy.

Advise women of childbearing age who take other antihypertensive treatments that
there is no evidence that such treatments carry a risk of congenital malformation.

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

Prevention of pre-eclampsia
In women with chronic hypertension, offer treatment with aspirin* (75 mg/day) from
12 weeks until the birth of the baby.

Treatment of hypertension
In pregnant women with chronic hypertension aim to keep blood pressure less than
150/100 mmHg.
In pregnant women with chronic hypertension do not use treatment to lower
diastolic blood pressure to less than 80 mmHg.
In pregnant women with end-organ damage secondary to chronic hypertension
offer treatment to keep blood pressure lower than 140/90 mmHg.
Refer pregnant women with secondary chronic hypertension for specialist
treatment.
In women with chronic hypertension, advise antihypertensive treatment dependent
on pre-existing treatment, side-effect profiles and teratogenicity.

Antenatal visits
In women with chronic hypertension, schedule additional antenatal visits on the
basis of the individual needs of the woman and her baby.

Timing of birth
For women with chronic hypertension whose blood pressure is lower than 159/109
mmHg with or without antihypertensive treatment, do not offer birth before 37
weeks.
For women with refractory severe chronic hypertension, offer birth before 37 weeks after a course of antenatal steroids has been completed.

Offer birth to women with chronic hypertension whose diastolic blood pressure is greater than 95 mmHg with or without antihypertensive treatment after 37+0 weeks.

Offer birth to women with chronic hypertension after 39+0 weeks.

Consider birth at any gestation when there is evidence of impending fetal death.

**Postnatal investigation, monitoring and treatment**

In women with chronic hypertension who have just given birth, measure blood pressure:
- daily while the woman is an inpatient
- 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 recently given birth, aim to keep blood pressure below 140/90 mmHg.

In women with chronic hypertension who have just given birth, continue use of antenatal antihypertensive treatment.

In women with chronic hypertension who have recently given birth, review long-term antihypertensive treatment 2 weeks after the birth.

If a woman has received methyldopa to treat chronic hypertension during pregnancy, stop within 2 days of birth and restart the antihypertensive treatment the woman was receiving before planning pregnancy.

In women with chronic hypertension, avoid diuretic treatment for hypertension if the woman is breastfeeding or expressing milk.

Advise women with chronic hypertension that the following commonly used drugs have no known adverse effects on babies receiving breast milk:
- labetalol
- nifedipine
- enalapril

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4 Methyldopa is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.

5 Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.

6 Nifedipine is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that it is contraindicated in pregnancy before week 20 and during breastfeeding, or that it must not be administered during the entire pregnancy and that the child should be weaned if treatment should be necessary during the lactation period, or that it should not be used in women who are or who may become pregnant and that it is not recommended during lactation, or that it should not be used in nursing mothers and women who are or who may become pregnant. Informed consent on the use of nifedipine in these situations should be obtained and documented.

7 Enalapril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.
Advise women with chronic hypertension that there is insufficient evidence on the safety in babies receiving breast milk of the following drugs that are commonly used to treat hypertension:

- captopril
- atenolol
- metoprolol
- chlorothiazide/hydrochlorothiazide.

In women with chronic hypertension, perform medical review at the postnatal visit (6–8 weeks after the birth).

Chapter 5 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.

Quantify proteinuria when there is 1+ or more on automated urinary dipstick.

Use 24-hour urine collection to quantify proteinuria.

Chapter 6 Management of pregnancy with gestational hypertension

Treatment of hypertension

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

In women with gestational hypertension, take account of the following risk factors when planning assessment and follow-up:

- age more than 40 years

---

8 Captopril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 2009) advises that it is contraindicated in the second and third trimesters of pregnancy and in lactation, and that is not recommended during the first trimester of pregnancy. Informed consent on the use of captopril in these situations should be obtained and documented.

9 Atenolol is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that its use in early pregnancy should be avoided, or that its use in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters and caution should be exercised when it is administered during pregnancy or to a woman who is breastfeeding. Informed consent on the use of atenolol in these situations should be obtained and documented.

10 Metoprolol is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that it should not be used in pregnancy or nursing mothers unless the physician considers that the benefit outweighs the possible hazard to the fetus/infant and breastfeeding is not recommended, or that it should not be used in pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the fetus/infant. Informed consent on the use of metoprolol in these situations should be obtained and documented.

11 Chlorothiazide/hydrochlorothiazide, which are already used widely in UK obstetric practice, are available only in combination products (e.g., combinations with captopril or enalapril, and the SPCs (August 2009) for the combination products advise the same contraindications and warnings in relation to pregnancy and lactation as for captopril or enalapril alone). Informed consent on the use of chlorothiazide/hydrochlorothiazide combination products in these situations should be obtained and documented.

12 Enalapril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.

13 Captopril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 2009) advises that it is contraindicated in the second and third trimesters of pregnancy and in lactation, and that is not recommended during the first trimester of pregnancy. Informed consent on the use of captopril in these situations should be obtained and documented.
• nulliparity
• pregnancy interval of more than 10 years
• family history of pre-eclampsia
• multiple pregnancy
• BMI more than 35
• gestational age at presentation
• previous history of pre-eclampsia or gestational hypertension
• pre-existing vascular disease
• pre-existing renal disease.
Manage gestational hypertension as described in the table below:

<table>
<thead>
<tr>
<th>Degree of hypertension</th>
<th>Mild hypertension (&lt;149/99 mmHg)</th>
<th>Moderate hypertension (150/100 to 159/109 mmHg)</th>
<th>Severe hypertension (160/110 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit to hospital</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Treat</td>
<td>No</td>
<td>Yes with oral labetalol\textsuperscript{14} to keep:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• diastolic blood pressure less than 100 mm Hg but more than 80 mm Hg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• systolic blood pressure less than 150 mm Hg</td>
<td></td>
</tr>
<tr>
<td>Measure blood pressure</td>
<td>Yes routinely not more than once a week</td>
<td>Yes at least twice a week</td>
<td>Yes at least four times a day</td>
</tr>
<tr>
<td>Test for proteinuria</td>
<td>Yes at each visit using automated dipsticks</td>
<td>Yes at each visit using automated dipsticks</td>
<td>Yes daily using automated dipsticks</td>
</tr>
<tr>
<td>Blood tests</td>
<td>No (none in addition to those for routine antenatal care)</td>
<td>Yes test urea electrolytes and request a full blood count, platelets, serum creatinine, transaminases, bilirubin</td>
<td>Yes test at presentation: full blood count, platelets, serum creatinine, transaminases, bilirubin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• do not carry out further blood tests if no proteinuria at subsequent visits.</td>
<td>• monitor weekly: full blood count, platelets, serum creatinine, transaminases, bilirubin</td>
</tr>
</tbody>
</table>

In women receiving outpatient treatment for severe gestational hypertension, 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.

In women with gestational hypertension, offer alternative antihypertensive treatment after considering side-effect profiles for the woman, fetus and neonate.

Do not use bed rest as a treatment for gestational hypertension.

**Timing of birth**

For women with gestational hypertension whose blood pressure is lower than 159/109 mmHg with or without antihypertensive treatment, do not offer birth before 37 weeks.

For women with refractory severe gestational hypertension, offer birth before 37 weeks after a course of antenatal steroids has been completed.

Offer birth to women with gestational hypertension whose diastolic blood pressure is greater than 95 mmHg with or without antihypertensive treatment after 37 + 0 weeks.

\textsuperscript{14} Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.
Offer birth to women with gestational hypertension after 39 + 0 weeks.

**Postnatal investigation, monitoring and treatment**

In women with gestational hypertension who have just given birth, measure blood pressure:
- daily while the woman is an inpatient
- between day 3 and day 5 after birth
- as clinically indicated if antihypertensive treatment is changed after birth.

In women with gestational hypertension who have recently given birth, aim to keep blood pressure below 140/90 mmHg.

In women with gestational hypertension who have just given birth, continue use of antenatal antihypertensive treatment.

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

For women with gestational hypertension who have recently 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.

For women who did not receive antihypertensive treatment and have recently given birth, start antihypertensive treatment if their blood pressure exceeds 150/100 mmHg.

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

Refer women who have had gestational hypertension and who still require antihypertensive treatment at the postnatal visit (6–8 weeks after the birth) for specialist assessment.

**Chapter 7 Management of pregnancy with pre-eclampsia**

**Treatment of hypertension**

Assess women with pre-eclampsia at each consultation; assessment should be performed by an appropriately trained healthcare professional.

Manage pre-eclampsia as described in the table below:

<table>
<thead>
<tr>
<th>Degree of hypertension</th>
<th>Mild hypertension (&lt;149/99 mmHg)</th>
<th>Moderate hypertension (150/100 to 159/109 mmHg)</th>
<th>Severe hypertension (160/110 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit to hospital</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treat</td>
<td>No</td>
<td>Yes with oral labetalol(^{16}) to keep</td>
<td>Yes with oral labetalol(^{16}) to keep</td>
</tr>
</tbody>
</table>

\(^{15}\) Methyldopa is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.
Timing of birth

Manage pregnancy in women with pre-eclampsia conservatively until 34 weeks.

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

Consultant obstetric staff should write a plan for fetal monitoring.

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 haematological, biochemical or clinical indications develop as specified in the consultant plan
- fetal indications develop as specified in the consultant plan.

Advise birth for women with severe pre-eclampsia after 34 weeks once their blood pressure is controlled and, if appropriate, a course of antenatal steroids has been completed.

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.

Advise 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 receive antihypertensive treatment and have just given birth, measure blood pressure:

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Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.
• at least four times a day while the woman is an inpatient
• 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 recently given birth, aim to keep blood pressure below 140/90 mmHg.

In women with pre-eclampsia who did not receive antihypertensive treatment and have recently given birth, start antihypertensive treatment for the first time if blood pressure is higher than 150/100 mmHg.

Ask women with pre-eclampsia who did not receive antihypertensive treatment and have recently given birth about severe headache and epigastric pain each time blood pressure is measured.

In women with pre-eclampsia who received antihypertensive treatment and have just 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 discharge from hospital until the woman is off treatment and has no hypertension.

In women with pre-eclampsia who have received antihypertensive treatment and have recently given birth, consider reducing antihypertensive treatment when their blood pressure falls below 140/90 mmHg.

In women with pre-eclampsia who have received antihypertensive treatment and have recently given birth, reduce antihypertensive treatment when blood pressure falls below 130/80 mmHg.

In women who have pre-eclampsia and remain on antihypertensive treatment 2 weeks after discharge from hospital, perform medical review.

In women who have had pre-eclampsia perform medical review at the postnatal visit (6–8 weeks after the birth).

Refer women who have had pre-eclampsia and who still require antihypertensive treatment at the postnatal visit (6–8 weeks after the birth) for specialist assessment.

---

Methyldopa is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.
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 if results are normal at 48-72 hours.

In women with pre-eclampsia, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated and at the postnatal visit (6-8 weeks after the birth) if biochemical and haematological indices are improving but stay within the abnormal range.

In women with pre-eclampsia, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated if biochemical and haematological indices are not improving relative to pregnancy ranges.

In women with pre-eclampsia, carry out a urine dipstick test at the postnatal visit (6-8 weeks after the birth).

In women with pre-eclampsia who have recently given birth, do not measure fluid balance when creatinine is within the normal range.

In women who still require antihypertensive treatment at the postnatal visit (6-8 weeks after the birth) carry out further evaluation of renal function if urine protein is 2+ or more.

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, do not carry out cardiotocography if fetal activity is normal.

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, do not carry out cardiotocography if fetal activity is normal.

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 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:

- a change in the woman’s perception of 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 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, inform 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 monitoring
- fetal indications for birth and whether and when antenatal steroids should be given
- discussion with neonatal paediatricians and obstetric anaesthetists.

**Women at high risk of pre-eclampsia**

In women who are at a high risk of pre-eclampsia, do not use uterine artery Doppler velocimetry.

Carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry starting at between 28 and 30 weeks (or 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 requiring birth before 34 weeks
- pre-eclampsia with a baby born <10th centile
- intrauterine death
- placental abruption.

In women who are at a high-risk of pre-eclampsia, do not carry out cardiotocography if fetal activity is normal.

**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**

Measure blood pressure hourly during labour in women with mild or moderate hypertension.

In women with hypertension in pregnancy, continue use of existing 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.

Advise operative birth in the second stage of labour for women with severe hypertension who have 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.

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

- hypertension and proteinuria and
- symptoms of severe headache or
- liver tenderness or
- visual disturbance or
- platelet count falling to below 100 x 10⁹ per litre or
- epigastric pain or vomiting or
- abnormal liver enzymes (ALT or AST rising to above 70 iu/litre) or
- signs of clonus or
- HELLP syndrome or
- papilloedema.

Use the Collaborative trial regimen for administration of magnesium sulphate:*
loading dose of 4 g should be given by infusion pump over 5–10 minutes, followed by a further infusion of 1 g/hour maintained for 24 hours after the last seizure.

- recurrent seizures should be treated with either a further bolus of 2 g magnesium sulphate* or an increase in the infusion rate to 1.5 g or 2.0 g/hour.

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

Consider using up to 500ml 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, 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 at 35-36 weeks.

**Corticosteroids in the management of HELLP syndrome**

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

**Fluid balance and volume expansion**

Do not use volume expansion for women with severe pre-eclampsia except when hydralazine is the antenatal antihypertensive.

In women with severe pre-eclampsia, limit total fluids to 80 ml/hour.

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18 Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.

19 Nifedipine is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that it is contraindicated in pregnancy before week 20 and during breastfeeding, or that it must not be administered during the entire pregnancy and that the child should be weaned if treatment should be necessary during the lactation period, or that it should not be used in women who are or who may become pregnant and that it is not recommended during lactation, or that it should not be used in nursing mothers and women who are or who may become pregnant. Informed consent on the use of nifedipine in these situations should be obtained and documented.
Operative birth (caesarean section versus induction of labour)

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

Indications for referral to critical care levels

Refer women with pre-eclampsia to the appropriate critical care setting using the following criteria:

<table>
<thead>
<tr>
<th>Level 3</th>
<th>Severe pre-eclampsia and needing ventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 2</td>
<td>Step down from level 3 of severe pre-eclampsia with any of the following complications:</td>
</tr>
<tr>
<td></td>
<td>- eclampsia</td>
</tr>
<tr>
<td></td>
<td>- HELLP syndrome</td>
</tr>
<tr>
<td></td>
<td>- haemorrhage</td>
</tr>
<tr>
<td></td>
<td>- hyperkalaemia</td>
</tr>
<tr>
<td></td>
<td>- severe oliguria</td>
</tr>
<tr>
<td></td>
<td>- coagulation support</td>
</tr>
<tr>
<td></td>
<td>- intravenous antihypertensive treatment</td>
</tr>
<tr>
<td></td>
<td>- initial stabilisation of severe hypertension</td>
</tr>
<tr>
<td></td>
<td>- evidence of cardiac failure</td>
</tr>
<tr>
<td></td>
<td>- abnormal neurology</td>
</tr>
<tr>
<td>Level 1</td>
<td>Mild or moderate pre-eclampsia</td>
</tr>
<tr>
<td></td>
<td>- Ongoing conservative antenatal management of severe pre-term hypertension</td>
</tr>
<tr>
<td></td>
<td>- Step-down therapy after the birth</td>
</tr>
</tbody>
</table>

Chapter 11 Advice at discharge from maternity care

Long-term risk of cardiovascular disease

Advise women who have had pre-eclampsia that they are at increased risk of developing high blood pressure and its complications in later life and that they should have their blood pressure measured annually.

Advise women who have had gestational hypertension that they should have their blood pressure measured at least every 5 years.

Long-term risk of end-stage renal disease

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

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20Taken from Intensive Care Society, Standards and Guidelines 2002.
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

Inform women that if they had gestational hypertension in their first pregnancy, their risk of developing:

- gestational hypertension in their next pregnancy is on average 1 in 3 (32%)
- pre-eclampsia in their next pregnancy is 1 in 33 (3%).

Inform women that if they had pre-eclampsia in their first pregnancy, their risk of developing:

- gestational hypertension in their next pregnancy is 1 in 4 (26%)
- pre-eclampsia in their next pregnancy is around 1 in 7 (14.5%)
- pre-eclampsia in their next pregnancy is 1 in 4 (25%) if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and 1 in 2 (55%) if it led to birth before 28-30 weeks.

Inter-pregnancy interval and recurrence of hypertensive disorders of pregnancy

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

Body mass index and recurrence of hypertensive disorders of pregnancy

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

1.3 Key priorities for research

Reducing the risk of hypertensive disorders in pregnancy

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

Why this is important

Pre-eclampsia and gestational hypertension represent common pregnancy complications. Although large studies on the use of calcium supplementation to prevent hypertensive disorders during pregnancy have been carried out, the variation in populations and calcium status at entry to the studies have 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. Randomised controlled trials are needed 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. The 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 outcomes (neonatal morbidity, infant growth and development).

Postnatal care of women with chronic hypertension

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 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 its 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.

**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.

**Treatment of hypertension**

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

**Why this is important**

Pre-eclampsia is a multisystem disorder, but it is not clear whether routine assessment of a range of biochemical or haematological parameters aids 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 that examine a range of parameters singly and serially (renal function, liver function, coagulation, measurement of proteinuria) in women with new 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 devised 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: 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 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 infant would have costs.
Randomised controlled trials should be carried out that compare policies of immediate planned birth between 34 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.

1.4 Research recommendations

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?

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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 have 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. Randomised controlled trials are needed 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. The 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 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 established chronic hypertension is inadequate to determine if one therapy would offer advantages over others. All drugs in common use have potential side effects and potential fetal and neonatal effects. As chronic hypertension becomes 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 preparations and compare between antihypertensives. 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.

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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 predictor of pre-eclampsia, but 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, renal 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. Trial should be stratified for risk factor.

Antihypertensives for the management of hypertension in the critical care setting

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

Why this is important

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

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

Corticosteroids in the management of HELLP syndrome

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

Why this is important

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

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

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 care pathway is presented in a separate file for consultation.
2 Development of the guideline

2.1 Hypertensive disorders of pregnancy

Hypertension during pregnancy is defined as a diastolic blood pressure greater than 90 mm Hg on two occasions more than 4 hours apart or a single diastolic blood pressure above 110 mm Hg. 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.

In addition, 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.

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%. The rate for gestational hypertension is almost certainly under-reported, with rates between 4.2% and 7.9% recorded. 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. 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%. 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, hypertension in pregnancy remains one of the leading causes of maternal death in
the UK, Europe and elsewhere. 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.

Maternal morbidity may be substantial 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, 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. A study from one region of the UK reported that 1 in 50 women with severe pre-eclampsia was admitted to intensive care.

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.

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, 1 in 20 (4.5%) stillbirths in infants without congenital abnormality occurred in women with pre-eclampsia. While this may be an improvement from the late 1990s (7%) it still represents a significant burden. A similar trend in the stillbirth rate has been seen in Sweden. Ten percent of women with severe pre-eclampsia give birth before 34 weeks. The contribution of pre-eclampsia to the overall preterm birth rate is substantial; 1 in 250 women in their first pregnancy will give birth before 34 weeks as a consequence of pre-eclampsia and 8-10% of all preterm births result from hypertensive disorders. Half of women with severe pre-eclampsia give birth preterm.

Small-for-gestational age (SGA) babies (mainly arising as a consequence 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.

There is national guidance on the care of women with severe pre-eclampsia or eclampsia and on screening for hypertensive disorders during pregnancy. 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, peripartum 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’, National Institute for Health and Clinical Excellence (NICE) clinical guideline 62)23
- 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 6223
- ‘Intrapartum care’, NICE clinical guideline 5524
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
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

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

For each clinical question, the highest available level of evidence was sought. Where appropriate, for example, if a systematic review, meta-analysis or RCT was identified to answer a question, studies of a weaker design were not considered. Where systematic reviews, meta-analyses and RCTs 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 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 and negative predictive values (PPVs and 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

<table>
<thead>
<tr>
<th>Level</th>
<th>Source of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+++</td>
<td>High-quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1++</td>
<td>Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2+++</td>
<td>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</td>
</tr>
<tr>
<td>2++</td>
<td>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</td>
</tr>
<tr>
<td>2+</td>
<td>Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytical studies (for example, case reports, case series)</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion, formal consensus</td>
</tr>
</tbody>
</table>

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.30 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 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 I)
- cost effectiveness of automated urinalysis compared to visual urinalysis in the quantification of proteinuria in women with gestational hypertension (see Appendix J)
- 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 K)
- 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 L).
Table 2.3 ‘2 × 2’ table for calculation of diagnostic accuracy parameters

<table>
<thead>
<tr>
<th>Reference standard positive</th>
<th>Reference standard negative</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test positive</td>
<td>b (false positive)</td>
<td>a+b</td>
</tr>
<tr>
<td>Test negative</td>
<td>d (true negative)</td>
<td>c+d</td>
</tr>
<tr>
<td>Total</td>
<td>a+c</td>
<td>b+d</td>
</tr>
</tbody>
</table>

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 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. [This paragraph will apply to the final published guideline.]

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 and neonatal outcomes.
Maternal outcomes

- Maternal death
- Pre-eclampsia
- Severe pre-eclampsia, eclampsia and HELLP syndrome
- Maternal complications (stroke, cerebral haemorrhage, myocardial infarction, renal failure, placental abruption, and pulmonary oedema)
- Admission to a high dependency unit (HDU) or intensive care unit (ICU)
- Need for antihypertensive medications

Neonatal 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)

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

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Systematic review (with homogeneity)(^a) of level-1 studies(^b)</td>
</tr>
<tr>
<td>Ib</td>
<td>Level-1 studies(^b)</td>
</tr>
<tr>
<td>II</td>
<td>Level-2 studies; systematic reviews of level-2 studies</td>
</tr>
<tr>
<td>III</td>
<td>Level-3 studies; systematic reviews of level-3 studies</td>
</tr>
<tr>
<td>IV</td>
<td>Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or ‘first principles’</td>
</tr>
</tbody>
</table>

\(^a\) 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 renal 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. 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

Four systematic reviews, one meta-analysis and one RCT were identified. The systematic reviews focused specifically on the reduction of risk of pre-eclampsia. In order to assess the effectiveness of different dosages of aspirin for the prevention of pre-eclampsia a subgroup analysis by dose was conducted which included studies from the original systematic review. The meta-analysis of individual-patient data on risk reduction for pre-eclampsia with antiplatelet agents provided subgroup analysis by risk. The RCT focused on a specific population of women with the converting enzyme DD and a history of pre-eclampsia. A 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. 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 evaluated the prevention of gestational hypertension (n=20,701). No statistically significant difference in the incidence of gestational hypertension in women receiving antiplatelet agents compared to women receiving placebo or no antiplatelet agents was found (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 reduced 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 reduced the risk of preterm birth before 37 weeks (RR=0.92, 95% CI 0.88 to 0.97) and the risk of fetal and neonatal death (RR=0.86, 95% CI 0.76 to 0.98).

A subgroup analysis of maternal risk for gestational hypertension and pre-eclampsia was conducted. Maternal risk was divided into moderate and high risk. High risk was defined as either women with chronic hypertension without superimposed pre-eclampsia or normotensive women with one or more of the following: previous severe pre-eclampsia, diabetes, chronic hypertension, renal 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 lowered the 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 more effective for reduction of pre-eclampsia risk in high-risk women than in moderate-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), reduced 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 showed a risk reduction (RR=0.70, 95% CI 0.51 to 0.95).

Similarly, there was a different effect in women receiving low-dose aspirin and women 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 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 subgroup analysis by dose of aspirin (mg/day) was conducted to assess the most effective dosage. The subgroups considered were 60mg, 75mg, 100mg and 150mg. The group receiving 60 mg aspirin per day showed no risk reduction (RR=0.92, 95% CI 0.84 to 1.00), as did the 100mg group (RR=0.71, 95% CI 0.50 to 1.02) and the 150mg group (RR=0.95, 95% CI 0.67 to 1.35); however 75mg aspirin per day showed a statistically significant reduction in risk of developing pre-eclampsia (RR=0.65, 95% CI 0.51 to 0.83).

A meta-analysis using individual-patient data assessed the effectiveness of antiplatelet agents (mainly aspirin) in risk reduction for pre-eclampsia.[37] This analysis included 32,217 women and their 32,819 babies. Overall the analysis showed a reduction in risk of developing pre-eclampsia (RR=0.90, 95% CI 0.84 to 0.97). In women having their first pregnancy and with any high-risk factor (such as pre-existing renal disease, diabetes, chronic hypertension or with a previous SGA infant), there was no 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 risk reduction (RR=0.89, 95% CI 0.81 to 0.99). There was no 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;31-39 of these, one study39 was excluded because it was not a cost effectiveness study leaving one study that met the inclusion criteria (a Health Technology Assessment (HTA) report by Meads et al 2008).31 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 reduces the occurrence of pre-eclampsia, preterm birth and neonatal mortality in women with risk factors. 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, renal disease or autoimmune disease) the effect is 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 pregnancies, 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, and although there is no statistical evidence of a 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 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. The data are clearest for women at high risk. The GDG defined high-risk women as those having one or more of the following: previous hypertensive disease during pregnancy, chronic renal disease, auto-immune disease such as systemic lupus erythematosis (SLE) or
antiphospholipid syndrome, type 1 or type 2 diabetes or chronic hypertension. Women with previous pre-eclampsia appeared to benefit most.

Moderate risk factors were poorly defined in the studies so it was not possible to provide objective advice about individual risk factors. However, the GDG considered that some women with moderate risk factors would benefit from aspirin, particularly if they had more than one of the following risk factors. The relevant risk factors are: first pregnancy, age 40 years or over, family history of pre-eclampsia, body mass index (BMI) more than 35 at first visit, and multiple pregnancy (see ‘Antenatal care’, NICE clinical guideline 62).

The dosage relationship is difficult to disentangle. The published systematic review combines studies with aspirin dosages of 60mg and 75mg and combines 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 dose available in the UK 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 appears to be a trend towards a greater effect if aspirin is given before 20 weeks. The GDG believes it is important to start using aspirin before that time. There is no conclusive evidence to support the most beneficial 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 renal disease
- autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome
- type 1 or type 2 diabetes
- chronic hypertension.

Offer women with more than one moderate risk factor for pre-eclampsia 75 mg of aspirin* daily from 12 weeks until birth of the baby. Factors indicating moderate risk are:
- first pregnancy
- age more than 40 years
- body mass index (BMI) more than 35 at first visit
- family history of pre-eclampsia
- multiple pregnancy.

3.3 Other pharmaceutical agents

Clinical effectiveness

Nitric oxide agents (glycerine trinitrate, L-arginine)

A systematic review of six RCTs, involving 310 women, investigated the effectiveness of nitric oxide for preventing pre-eclampsia. 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 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 two studies and the quality uncertain.

Nitric oxide donors or precursors were compared with either placebo or no intervention. There was no statistically significant effect for nitric oxide (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 and those receiving placebo or no treatment was found (RR=0.10, 95% CI 0.01 to 1.87).

Progestrone

A systematic review of two RCTs, involving 296 women, evaluated the preventive effect of progesterone on pre-eclampsia. 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 systematic review of five studies, involving 1,836 women, evaluated the effect of diuretics for preventing pre-eclampsia. 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 recurrence 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 (LWMH) on the recurrence rate of pre-eclampsia. 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 renal 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. No reduction in the rate of hypertensive disorders has been demonstrated.

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

There is limited good-quality evidence on the use of LMWH in the prevention of hypertensive disorders during pregnancy. The evidence shows 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**

Existing evidence suggests no demonstrable 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.

**Recommendations**

Do not use the following for the prevention of hypertensive disorders during pregnancy:

- nitric oxide donors
- progesterone
- diuretics
3.4 Nutritional supplements

Clinical effectiveness

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.40,41,43,44 [EL=1+] A prospective cohort study was also identified in relation to the use of folic acid supplementation.42 [EL=2+]

Calcium

A systematic review of 12 RCTs, involving 15,206 women, evaluated the effectiveness of calcium in risk reduction for pre-eclampsia.40 [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 or no treatment (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). However one study (n=8,302) investigating severe pre-eclampsia showed no statistically significant effect (RR=0.74, 95% CI 0.48 to 1.15).

A subgroup analysis showed no statistically significant effect of calcium supplementation on the incidence of pre-eclampsia in women with adequate dietary calcium, regardless of sample size. Two small studies (n=230) of women with adequate baseline dietary calcium showed no statistically significant effect of calcium supplementation (RR=0.26, 95% CI 0.04 to 1.50), as did two large studies (n=4,792) of women with adequate baseline dietary calcium (RR=0.70, 95% CI 0.33 to 1.46).

Five small studies (n=675) involving women with low baseline dietary calcium showed a strong effect of calcium supplementation on the incidence of pre-eclampsia (RR=0.21, 95% CI 0.12 to 0.38), whereas the results for two large studies (n=9,479) involving women with a low baseline calcium showed no statistically significant reduction in the incidence of pre-eclampsia (RR=0.89, 95% CI 0.74 to 1.09).

Magnesium

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

Antioxidants

A systematic review of 10 RCTs, involving 6,533 women, evaluated the risk reduction effects of antioxidants on pre-eclampsia.41 [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 or severe hypertension. 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), and two studies (n=4,272) investigated severe hypertension (RR=1.39, 95% CI 0.85 to 2.30). 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. 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. 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 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. 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 systematic review of one study involving 100 women investigated the effectiveness of garlic for risk reduction for pre-eclampsia. 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 effect is influenced by trial size. 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 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 result.

**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 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 beneficial effects of calcium supplementation appear in the smaller studies, making it difficult to determine the true effect. The benefits are also 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 conflicting, and the GDG’s view is that a recommendation for additional calcium for women at risk in a UK setting cannot be justified. However the magnitude of
the effect in some studies indicates the need for further research in women with risk factors for hypertension in pregnancy who have adequate calcium diets.

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.

**Recommendations**

Do not use the following supplementation to prevent 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 have 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. Randomised controlled trials are needed 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. The 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 outcomes (neonatal morbidity, infant growth and development).

### 3.5 Diet

**Clinical effectiveness**

Salt restriction

An RCT involving 361 women evaluated the effect of dietary salt intake during pregnancy for the prevention of pre-eclampsia in women with gestational hypertension. 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 renal 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 low-sodium group and the women who continued 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

Salt restriction

There is limited good-quality evidence that 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 evidence that salt restriction in women with gestational hypertension prevented pre-eclampsia.

Recommendations

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

3.6 Lifestyle

Clinical effectiveness

Rest

A 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.47 [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.

Exercise
A 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. 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 renal disease, diabetes, multiple pregnancy, and those who undertook vigorous exercise with rating of perceived exertion (RPE) >14 were excluded. The other study (n=45) 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).

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

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. 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 3.6 kg versus ≤ 4.5kg 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.

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.

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.
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. They 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) 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.

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. 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 with 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 USA\textsuperscript{51} [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.\textsuperscript{52} [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 pregnancy\textsuperscript{53}[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 renal 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.\textsuperscript{54}[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 patients 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>
<thead>
<tr>
<th>Drug</th>
<th>Route</th>
<th>Safety data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Oral</td>
<td>- Mild hypotension in babies 2 days life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labetalol</td>
<td>Oral / IV</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Rare mild hypotension in first 24hrs of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Very rare hypoglycaemia</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Oral</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Low birth weight/placental weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Decreased fetal heart rate described</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Oral</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>Oral</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Pindolol</td>
<td>Oral</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Alpha blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prazosin</td>
<td>Oral</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Oral</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Oral</td>
<td>- No reports</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Oral / IV</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>Oral</td>
<td>- Possible association with congenital abnormalities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Possible neonatal thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Possible neonatal hypoglycaemia/hypovolaemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Possible maternal/fetal electrolyte imbalances</td>
</tr>
<tr>
<td>Bendrofluazide</td>
<td>Oral</td>
<td>- No adverse fetal effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Maternal hypovolaemia</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Oral / IV</td>
<td>- No obvious effects</td>
</tr>
<tr>
<td>Vasodilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>IV</td>
<td>- No obvious association with congenital abnormalities</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>IV</td>
<td>- May inhibit uterine contractions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Profound maternal hypotension possible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Neonatal hyperglycaemia reported</td>
</tr>
</tbody>
</table>

**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, renal 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**

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.

Advise women of childbearing age 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 alternative antihypertensive treatment with their healthcare professional if they are planning pregnancy.

Review antihypertensive treatments for women taking ACE inhibitors or ARBs when they become pregnant (preferably within 2 working days of notification of pregnancy) and discuss alternatives.

Advise women of childbearing age 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 alternative antihypertensive treatment with their healthcare professional if they are planning pregnancy.

Advise women of childbearing age who take other antihypertensive treatments that there is no evidence that such treatments carry a risk of congenital malformation.

**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).

**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) in relation to dietary salt intake.

**Recommendations**

Encourage women with chronic hypertension to keep their dietary sodium intake low, either by reducing or substituting sodium salt, as 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. The study involved women at risk of developing pre-eclampsia, gestational hypertension or IUGR based on their previous pregnancy history, a pre-existing medical condition (e.g. renal 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.

Sub-group 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).

Evidence statement

A meta-analysis of individual-patient data 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 felt that it should be as soon as possible after pregnancy has been diagnosed, and preferably from 12 weeks.

Recommendations

In women with chronic hypertension, offer treatment with aspirin* (75 mg/day) from 12 weeks until the birth of the baby.

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. An RCT involving 300 women was conducted in the USA to compare the effect of methyldopa and labetalol with no treatment in chronic hypertension. 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.

Labetalol

An RCT investigated the effectiveness of labetalol and methyldopa in chronic hypertension. 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. 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.[58][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 treat ment
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.[59][EL=1-] Inclusion criteria were: a documented history of hypertension (blood pressure
\( \geq 140/90 \text{ mmHg} \)) 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 RCT[^60] [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 renal 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 born preterm (RR 0.52; 95% CI 0.28 to 0.99). There were no significant differences between groups in terms of intraterine fetal death, admission to NICU, or fetal growth restriction.

One multicentre RCT[^61] [EL 1+] conducted in Canada, New Zealand, Australia and the UK compared 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 (160 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 ±3.0 versus 36.3 weeks ±3.3, p=0.278), serious perinatal complications (13.6% versus 21.5%; RR=0.63, 95% CI 0.30 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 2500grams (34.9% versus 49.2%, RR=0.71, 95% CI0.47 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).

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.

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.62[EL=1+] Two hundred and eighteen women with singleton pregnancies and blood pressure ≥ 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 ≥ 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 having bed rest and those 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. The evidence available suggests that treatment reduces the risk of severe hypertension but not the development of proteinuria.

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.

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. Women with evidence of end-organ damage from hypertension will need a lower target blood pressure than women without these changes in line
with 'Hypertension', NICE clinical guideline 34,28 which includes the following recommendations:

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

Bed rest
The evidence in relation to bed rest comes from a small RCT showing no effect of such rest.

Recommendations
In pregnant women with chronic hypertension aim to keep blood pressure less than 150/100 mmHg.
In pregnant women with chronic hypertension do not use treatment to lower diastolic blood pressure to less than 80 mmHg.
In pregnant women with end-organ damage secondary to chronic hypertension offer treatment to keep blood pressure lower than 140/90 mmHg.
Refer pregnant women with secondary chronic hypertension for specialist treatment.
In women with chronic hypertension, advise 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 established chronic hypertension is inadequate to determine if one therapy would offer advantages over others. All drugs in common use have potential side effects and potential fetal and neonatal effects. As chronic hypertension becomes 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 preparations and compare between antihypertensives. 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 study [63] 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 study [64] 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 studies [65-67] 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, renal disease, habitual abortion).

Using resistance index gave a sensitivity of 78-97% and specificity of 42-71% for prediction of pre-eclampsia. One study [65] (n=116) reported data on the use of resistance index in predicting IUGR, with a sensitivity of 84% and specificity of 39%.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Demographic characteristics</th>
<th>GA</th>
<th>Index</th>
<th>Pre-eclampsia</th>
<th>IUGR</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caruso 1996</td>
<td>Country: Italy 63</td>
<td>N=42 chronic hypertension: 37 mild (BP 140-159/90-109 mmHg), 5 severe (BP&gt;160/110 mmHg). Age 32(23-44)</td>
<td>23-24 wks</td>
<td>RI: abnormal &gt; 90th percentile Reference group: 1,084 healthy pregnant women</td>
<td>For high risk women: Sens: 78% Spec: 45% PPV: 28% NPV: 88%</td>
<td>Exclusion: autoimmune disease, fetal chromosomal abnormalities, Rh isoimmunisations Antihypertensive therapy was discontinued and restarted if BP&gt;160/110 mmHg. Endpoints: SPE</td>
</tr>
<tr>
<td>Parretti 2003</td>
<td>Country: Italy 65</td>
<td>N=144, previous PET (n=87), previous stillbirth (n=22), previous abrupto placenta (n=11), previous fetal growth restriction (n=24) Age: 34.5 (27-41), gravidity 2(2-3), parity: 1(1-2)</td>
<td>24 wks</td>
<td>RI: abnormal ≥ 0.58</td>
<td>Sens: 77.6% Spec: 44.4% PPV: 90.1%</td>
<td>Not reported Exclusion: smoking, renal disease, CVD, DM, multiple pregnancy, fetal chromosomal abnormalities, or if already on low-dose aspirin PE= BP&gt;140/90 mmHg, proteinuria &gt;0.3 g/24h. Endpoint: PE</td>
</tr>
<tr>
<td>Caforio 1999</td>
<td>Country: Italy 66</td>
<td>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± 4.8 yrs</td>
<td>N=249 at 22-24 wks</td>
<td>RI: abnormal &gt; 90th percentile</td>
<td>Sens: 97% Spec: 71% PPV: 99%</td>
<td>77% 72% 37% 94%(Endpoint: birthweight &lt;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</td>
</tr>
<tr>
<td>Coleman 2000</td>
<td>Country: New Zealand 67</td>
<td>N=116, CH (n=69), previous recurrent PE (n=24), previously early-onset PE requiring delivery at ≤ 32 weeks (n=25), previous placental abruption (n=10), renal disease (n=40), SLE (n=13), antiphospholipid syndrome (n=5) Age: 31 (19-43) yrs. 31/116 were nulliparous and 18% smoked during pregnancy.</td>
<td>22-24 wks</td>
<td>RI: any abnormal &gt;0.58 Bilateral notch</td>
<td>Sens: 91% Spec: 42% PPV: 92% NPV: 36%</td>
<td>84% 30% 33% 87% 36% 89% 53% 79% Exclusion: multiple pregnancies and pregnancies with recognised fetal abnormalities. Endpoint: PE * Data for Both RI &gt;0.58, any notch, and Any RI and any notch are also reported.</td>
</tr>
</tbody>
</table>
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

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

**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 individual patient management. 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 visits

The frequency of antenatal visits for women with chronic hypertension cannot be specified as the care of each pregnancy needs to be individualised. The only evidence on antenatal schedules is found in ‘Antenatal care’, NICE clinical guideline 62 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 visits on the basis of the individual needs of the woman and her baby.

4.7 Timing of birth

Clinical effectiveness

Maternal indications

No specific evidence was identified for timing of birth in women with chronic hypertension but the GDG considered that the advice on timing of birth should be the same as that given to women with gestational hypertension (see Section 6.6). If proteinuria develops then the management would become that described for women with pre-eclampsia (see Chapter 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. The timing of birth in women with chronic hypertension is, therefore, more likely to be for 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 arise more commonly in women with chronic hypertension.

Recommendations

For women with chronic hypertension whose blood pressure is lower than 159/109 mmHg with or without antihypertensive treatment, do not offer birth before 37 weeks.

For women with refractory severe chronic hypertension, offer birth before 37 weeks after a course of antenatal steroids has been completed.

Offer birth to women with chronic hypertension whose diastolic blood pressure is greater than 95 mmHg with or without antihypertensive treatment after 37+0 weeks.

Offer birth to women with chronic hypertension after 39+0 weeks.

Consider birth at any gestation when there is evidence of impending fetal death.
4.8 Postnatal investigation, monitoring and treatment

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

Frequency of observations or investigations

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

Choice of antihypertensive treatment

No evidence in relation to choice of antihypertensive treatment was identified.

Antihypertensive drugs and breastfeeding

The evidence identified in relation to antihypertensive drugs and breastfeeding is presented in Table 4.4 (further details are presented in Appendices M and N).
### Table 4.4 Safety profiles for commonly used antihypertensives during breastfeeding

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Patients</th>
<th>Dose used</th>
<th>Steady-state level</th>
<th>Milk/plasma ratio</th>
<th>Effects on infant</th>
<th>Relative infant dose</th>
<th>Reported paediatric concerns</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methyldopa</strong></td>
<td>Space for 21</td>
<td>3</td>
<td>500-100 mg/day po</td>
<td>1.02 ± 0.93 µg/ml</td>
<td>0.22</td>
<td>In 2 of the 3 breast-fed infants, plasma levels were undetectable (&lt;0.05 µg/ml) 6hrs after administration of the drug, but in one infant plasma concentration was 0.09 µg/ml 10 hrs after maternal dosing. It is estimated that when the mother receives 1 gm methyldopa a day, the average cumulative load to the breastfed infant would be 195 µg, or 0.02% of the maternal dose.</td>
<td>0.11&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Nil&lt;sup&gt;66,70&lt;/sup&gt;</td>
</tr>
<tr>
<td>Hauser 1985&lt;sup&gt;72&lt;/sup&gt;</td>
<td>1</td>
<td>250 mg (1x)</td>
<td>2.5 hrs after dose: 1450 ng/ml</td>
<td>-</td>
<td>No adverse clinical effects were noted during the 3-month follow up period of the infant. Methyldopa is excreted in human milk in concentrations that probably do not harm the breast-fed infant.</td>
<td>0.57%&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Nil&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Only small quantities excreted into breast milk&lt;sup&gt;69,74&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Labetalol</strong></td>
<td>Space for 21</td>
<td>3</td>
<td>600-1200 mg/day</td>
<td>228± 178 µg/l</td>
<td>220± 253µg/l</td>
<td>1.5</td>
<td>No consistent pattern in the milk/plasma ratio. A measurable plasma concentration in one infant. At the end of the dose interval, the concentration was similar to that in the mother.</td>
<td>0.57%&lt;sup&gt;66&lt;/sup&gt;</td>
</tr>
<tr>
<td>Taylor 1981&lt;sup&gt;75&lt;/sup&gt;</td>
<td>1</td>
<td>20 mg twice a day</td>
<td>2.25 hrs after last dose: 17 ng/ml</td>
<td>2.25 hrs after last dose: 4 ng/ml</td>
<td>0.24</td>
<td>The estimated intake of propranolol by infant was 3 µg daily</td>
<td>0.29%&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Nil&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Smith 1983&lt;sup&gt;76&lt;/sup&gt;</td>
<td>3</td>
<td>40 mg q.i.d</td>
<td>711± 49 ng/ml (peak)</td>
<td>429 ± 28 ng/ml (peak)</td>
<td>0.60</td>
<td>None (30 day follow up for infant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bauer 1979&lt;sup&gt;77&lt;/sup&gt;</td>
<td>9</td>
<td>20 mg b.i.d</td>
<td>17 ng/ml (peak)</td>
<td>4 ng/ml (peak)</td>
<td>0.24</td>
<td>No changes in HR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thorley 1983&lt;sup&gt;78&lt;/sup&gt;</td>
<td>5</td>
<td>40 mg b.i.d</td>
<td>2hrs after dose: 54 ± 14 ng/ml</td>
<td>2hrs after dose: 27 ± 5 ng/ml</td>
<td>2.0</td>
<td>None of the babies showed any clinical signs of beta-blockade</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atenolol</strong></td>
<td>Space for 21</td>
<td>8</td>
<td>50 mg</td>
<td>0.36 µg/ml</td>
<td>1.3 µg/ml</td>
<td>3.6</td>
<td>Level in infant plasma undetectable (&lt;10 ng/ml); no bradycardia or lethargy</td>
<td>6.6%&lt;sup&gt;69&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drug</td>
<td>Reference</td>
<td>Dose</td>
<td>Maternal Plasma Levels</td>
<td>Infant Plasma Levels</td>
<td>Adverse Effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>------</td>
<td>------------------------</td>
<td>----------------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Kulas 1984</td>
<td>100 mg</td>
<td>0.62 µg/ml (peak)</td>
<td>1.8 µg/ml (peak)</td>
<td>None of the babies showed any clinical signs of beta-blockade.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thorley 1983</td>
<td>100 mg/day</td>
<td>2hrs after dose: 712 ± 77 ng/ml</td>
<td>630 ± 121 ng/ml</td>
<td>1.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kulas 1984</td>
<td>100 mg (x1)</td>
<td>1658 ± 531 nmol/l</td>
<td>3512 ± 848 nmol/l</td>
<td>2.11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Schmimmel 1989</td>
<td>50 mg b.i.d</td>
<td>1.5 hr after dose: 469 ng/ml</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kulas 1984</td>
<td>100 mg (x1) or 50 mg (x2)</td>
<td>99 ± 37 nmol/l</td>
<td>281 ± 103 nmol/l</td>
<td>2.83</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Manninen 1991</td>
<td>10 mg t.i.d</td>
<td>12.04 ± 4.0 ng/ml</td>
<td>4.1 ± 0.8 ng/ml</td>
<td>0.34</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Penny 1989</td>
<td>20 mg</td>
<td>43 ng/ml (peak)</td>
<td>46 ng/ml (peak)</td>
<td>1.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enalapril</td>
<td>Redman 1990</td>
<td>20 mg po (x1)</td>
<td>123± 28 ng/ml (peak)</td>
<td>1.74± 2.41 ng/ml (peak)</td>
<td>0.014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Devin 1981</td>
<td>100 mg t.i.d (7 doses)</td>
<td>133.4 ± 713.1 ± 140.6 ng/ml (peak)</td>
<td>2.9 ± 4.7± 0.7 ng/ml (peak)</td>
<td>0.02 (peak)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verapamil</td>
<td>Anderson 1987</td>
<td>80 mg tds</td>
<td>42.9 ng/ml</td>
<td>25.8 ng/ml</td>
<td>0.60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Maternal plasma levels are small, and so infant dose remains low. Manufacturer suggests avoid.
<table>
<thead>
<tr>
<th>Hydralazine (HDZ)</th>
<th>Liedholm 1982</th>
<th>1</th>
<th>50 mg t.i.d</th>
<th>2 h after a.m. dose: 580 nmol/l (active HDZ)</th>
<th>2 h after a.m. dose: 792 nmol/l (active HDZ)</th>
<th>1.4</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Miller 982</td>
<td>1</td>
<td>50 mg</td>
<td>280 ng/ml (peak)</td>
<td>120 ng/ml (peak)</td>
<td>0.43</td>
<td>No detectable levels (&lt;1 ng/ml); electrolytes normal in infant</td>
</tr>
<tr>
<td></td>
<td>Werthmann 1972</td>
<td>11</td>
<td>500 mg (x1)</td>
<td>&lt; 1 µg/ml</td>
<td>&lt;1 µg/ml</td>
<td>-</td>
<td>No infants studied</td>
</tr>
<tr>
<td></td>
<td>Mulley 1978</td>
<td>7</td>
<td>50 mg</td>
<td>6.54 ± 1.86 µg/ml (peak)</td>
<td>0.37 ± 0.27 µg/ml (peak)</td>
<td>0.06</td>
<td>No infants studied</td>
</tr>
</tbody>
</table>

Hydrochlorothiazide

<table>
<thead>
<tr>
<th>Hydrochlorothiazide</th>
<th>Miller 982</th>
<th>1</th>
<th>50 mg</th>
<th>280 ng/ml (peak)</th>
<th>120 ng/ml (peak)</th>
<th>0.43</th>
<th>No detectable levels (&lt;1 ng/ml); electrolytes normal in infant</th>
</tr>
</thead>
</table>

Chlorothiazide

<table>
<thead>
<tr>
<th>Chlorothiazide</th>
<th>Werthmann 1972</th>
<th>11</th>
<th>500 mg (x1)</th>
<th>&lt; 1 µg/ml</th>
<th>&lt;1 µg/ml</th>
<th>-</th>
<th>No infants studied</th>
</tr>
</thead>
</table>

Chlorthalidone

<table>
<thead>
<tr>
<th>Chlorthalidone</th>
<th>Mulley 1978</th>
<th>7</th>
<th>50 mg</th>
<th>6.54 ± 1.86 µg/ml (peak)</th>
<th>0.37 ± 0.27 µg/ml (peak)</th>
<th>0.06</th>
<th>No infants studied</th>
</tr>
</thead>
</table>

American Academy of Paediatrics classifies as compatible with breastfeeding.
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 to 5 days after 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. As for pregnancy-related hypertensive disorders (see Chapters 6 and 7), the GDG’s view is that a formal medical review for women with chronic hypertension at the normal (6-8 week) postnatal visit would be useful.

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

There is no evidence in relation to effectiveness of postnatal drug use and efficacy in the postnatal period for women with chronic hypertension and therefore the GDG’s view is that antenatal antihypertensive treatment should continue.

If methyldopa has been used antenatally, its well recognised association with clinical depression should be remembered, and the GDG’s view is that its use should be stopped within 2 days of the birth where feasible.

The GDG is aware that the recent 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) suggests the preferential use of methyldopa in breastfeeding women, and that ACE inhibitors should not be used in these women. However, there is very little good evidence on drugs and breastfeeding, particularly for clinical outcomes, and most commonly used antihypertensive drugs appear to be safe. If a particular drug for chronic hypertension is deemed necessary to protect the woman’s health then there does not appear, to the GDG, to be strong grounds for withholding that drug or using a less effective treatment. The priority is to ensure effective blood pressure control and wellbeing in the woman and to reinforce general advice to encourage and support breastfeeding.

Recommendations

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

- daily while the woman is an inpatient
- 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 recently given birth, aim to keep blood pressure below 140/90 mmHg.

In women with chronic hypertension who have just given birth, continue use of antenatal antihypertensive treatment.

In women with chronic hypertension who have recently given birth, review long-term antihypertensive treatment 2 weeks after the birth.
If a woman has received methyldopa \(^{22}\) to treat chronic hypertension during pregnancy, stop within 2 days of birth and restart the antihypertensive treatment the woman was receiving before planning pregnancy.

In women with chronic hypertension, avoid diuretic treatment for hypertension if the woman is breastfeeding or expressing milk.

Advise women with chronic hypertension that the following commonly used drugs have no known adverse effects on babies receiving breast milk:

- labetalol \(^{23}\)
- nifedipine \(^{24}\)
- enalapril \(^{25}\)
- captopril \(^{26}\)
- atenolol \(^{27}\)
- metoprolol \(^{28}\)
- chlorothiazide/hydrochlorothiazide \(^{29}\)

\(^{22}\) Methyldopa is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.

\(^{23}\) Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.

\(^{24}\) Nifedipine is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that it is contraindicated in pregnancy before week 20 and during breastfeeding, or that it must not be administered during the entire pregnancy and that the child should be weaned if treatment should be necessary during the lactation period, or that it should not be used in women who are or who may become pregnant and that it is not recommended during lactation, or that it should not be used in nursing mothers and women who are or who may become pregnant. Informed consent on the use of nifedipine in these situations should be obtained and documented.

\(^{25}\) Enalapril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.

\(^{26}\) Captopril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.

\(^{27}\) Atenolol is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that its use in early pregnancy should be avoided, or that its use in women who are, or may become, pregnant requires that the anticipated benefit be weighed against the possible risks, particularly in the first and second trimesters and caution should be exercised when it is administered during pregnancy or to a woman who is breastfeeding. Informed consent on the use of atenolol in these situations should be obtained and documented.

\(^{28}\) Metoprolol is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that it should not be used in pregnancy or nursing mothers unless the physician considers that the benefit outweighs the possible hazard to the fetus/infant and breastfeeding is not recommended, or that it should not be used in pregnancy or lactation unless it is considered that the benefit outweighs the possible risk to the fetus/infant. Informed consent on the use of metoprolol in these situations should be obtained and documented.

\(^{29}\) Chlorothiazide/hydrochlorothiazide, which are already used widely in UK obstetric practice, are available only in combination products (e.g. combinations with captopril or enalapril, and the SPCs (August 2009) for the combination products advise the same contraindications and warnings in relation to pregnancy and lactation as for captopril or enalapril alone). Informed consent on the use of
Advise women with chronic hypertension that there is insufficient evidence on the safety in babies receiving breast milk of the following drugs that are commonly used to treat hypertension:

- ARBs
- amlodipine
- ACE inhibitors other than enalapril\(^{30}\) and captopril.\(^{31}\)

In women with chronic hypertension, perform medical review at the postnatal visit (6–8 weeks 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 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 its 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.

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\(^{30}\) Enalapril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.

\(^{31}\) Captopril is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 2009) advises that it is contraindicated in the second and third trimesters of pregnancy and in lactation, and that is not recommended during the first trimester of pregnancy. Informed consent on the use of captopril in these situations should be obtained and documented.
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 review[92 [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 renal 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 LRs were also found (LR+ 3.48, 1.66 to 7.27; LR- 0.6, 0.45 to 0.8).
A well conducted prospective study carried out in the UK included 171 pregnant women at 20 weeks or later and new-onset hypertension. 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 LRs were 51% (95% CI 39% to 62%), 78% (95% CI 68% to 86%), 2.27 (95% CI 1.47 to 3.51) and 0.64 (95% CI 0.49 to 0.82), respectively.

Another well conducted prospective study carried out in South Africa investigated 198 pregnant women who presented with hypertension at 28-34 weeks. 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 review 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 study conducted in the UK 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 this model are summarised below and full details are provided in Appendices I and J.
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\(^2\) 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) fail. 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 review\(^2\) [EL Ia] investigated the value of point-of-care dipstick urinalysis in the prediction of significant proteinuria (see Table 5.1).

**Table 5.1 Summary of Waugh et al’s (2004) systematic review\(^2\)**

<table>
<thead>
<tr>
<th>Reference Cut Off</th>
<th>Type of Dipstick</th>
<th>Proteinuria Level</th>
<th>Predictive Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg/24hrs</td>
<td>Visual</td>
<td>≥1+</td>
<td>Sensitivity 55%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity 84%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV 72%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV 30%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LR+ 3.48 (95% CI 1.66 to 7.27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LR- 0.6 (95% CI 0.45 to 0.8)</td>
</tr>
<tr>
<td>6 studies n=1,738</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Automated</td>
<td></td>
<td>≥1+</td>
<td>Sensitivity 82%</td>
</tr>
<tr>
<td>1 study n=171</td>
<td></td>
<td></td>
<td>Specificity 81%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PPV 77.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NPV 15.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LR+ 4.27 (95% CI 2.78 to 6.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LR- 0.22 (95% CI 0.14 to 0.36)</td>
</tr>
</tbody>
</table>
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. One study [EL=II] was conducted in Thailand, one [EL=III] was conducted in the USA 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. Women included in this study had either a resting blood pressure of ≥ 140/90 mmHg after 20 weeks, or chronic hypertension before 20 weeks with new-onset proteinuria. Women with renal 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 LRs derived from the reported sensitivity and specificity were 6.75 and 0.22 respectively.

A study conducted in the USA investigated the diagnostic accuracy of total urine protein measured in a 12-hour urine collection compared to total protein measured in a 24-hour collection. 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. Included patients 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 >150mg. Sensitivity was 96% and specificity 100%. CIs were not calculated because one cell contained the value zero.

One prospective diagnostic study [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 patients (gestational age ≥ 20 weeks) who had provided 24-hour urine sample for protein and creatinine clearance as requested by their physicians to rule out pre-eclampsia. Women with chronic hypertension, chronic renal disease, pathological vaginal discharge, urinary tract infection, patients 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, and an Italian study [EL=III] examined the diagnostic value of 24-hour urine microalbumin excretion measured in a 24-hour sample.

A well conducted UK prospective study included 171 women at 20 weeks or more and new-onset hypertension. 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 LRs were 49% (95% CI 38% to 61%), 83% (95% CI 74% to 90%), 2.9 (95% CI 1.76 to 4.78) and 0.61 (95% CI 0.48 to 0.78), respectively.

Another Italian study investigated the diagnostic accuracy of the albumin excretion rate, including 108 pregnant hypertensive women, of whom 40 (37%) had chronic hypertension.98 [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 review99 [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 specific  
ity of 94%, a positive LR of 15.7 and a negative LR of 0.05  
pared 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  
00%, a positive LR of infinity, and negative LR of 0.05 compared to 24- 
hour albuminuria.

**Evidence statement**

One systematic review\(^{99}\) [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>
<thead>
<tr>
<th>Ratio investigated</th>
<th>Study characteristics</th>
<th>Results</th>
</tr>
</thead>
</table>
| Spot protein: creatinine ratio      | 11 studies with 8 cut off points: (median 24 mg/mmol; 17-57 mg/mmol)                   | Sensitivity: Median 84% (range 78-90%); Specificity: Median 76% (range 73-80%);  
(+ ) LR: Median 3.53 (range 2.83 to 4.49); (-) LR: Median 0.21 (range 0.13 to 0.31)  
Cut-off: 30 mg/mmol (9 studies; 1003 women) |
| Spot albumin: creatinine ratio      | Cut-off: 2 mg/mmol                                                                     | Sensitivity: 94%; Specificity: 94%; (+ ) LR: 15.7; (-) LR: 0.06         |
|                                     | Cut-off: 27 mg/mmol                                                                   | Sensitivity: 95%; Specificity: 100%; (+ ) LR: infinity; (-) LR: 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 LRs, 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 reading device for measuring urinary protein levels by the dipstick test to diagnose pre-eclampsia in a secondary care setting.

Quantify proteinuria when there is 1+ or more on automated urinary dipstick.

Use 24-hour urine collection to quantify proteinuria.

**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 3 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 Assessment of risk of future pre-eclampsia or morbidity

Clinical effectiveness

Clinical risk factors

Evidence on risk factors for pre-eclampsia is discussed in `Antenatal care', NICE clinical guideline 62.23

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+] 100 The retrospective analysis (n=661) included patients initially diagnosed as having gestational hypertension, and the prospective study (n=184) women with gestational hypertension. Both excluded women with essential hypertension, renal disease or other secondary causes of hypertension.
Pre-eclampsia was defined as one or more of the following: proteinuria ≥ 300 mg/day (or persistently ≥ 2+ on dipstick urinalysis), renal impairment (plasma creatinine ≥ 100 μmol/L), hepatic dysfunction (aspartate transaminase ≥ 50 IU/L and or severe persistent epigastric pain), haematological abnormalities (haemolysis and/or platelet count < 150x109/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 patients 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 case-control study [EL 2+] was conducted in the US 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. 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 (Anumba et al) [EL II] conducted in the UK studied 560 women with suspected gestational hypertension. 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 significant LRs (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 significant LRs.

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

Serum uric acid

One study [EL II] and two studies [EL=III] investigated the diagnostic value of serum uric acid using different reference standards.

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. 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 S.D., which was 0.27mmol/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. 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 400 μmol/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 350 μmol/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. [EL II] (see description in 4.3.2) 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 significant 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 260 mmol/L, the sensitivity was 65%, specificity 47% with significant 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. All patients 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 x 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 x 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. [EL II] (see description in 4.3.2) showed that platelet count is not a significant predictor of pre-eclampsia in women suspected of having gestational hypertension.

Evidence statement

One evidence level III study showed platelet count to be of little diagnostic value. The reference test used was 1+ or greater on dipstick. The sensitivity was below 10% and specificity 92% when using a threshold of 150 x 10^9/l. Using a higher threshold (200 x 10^9/l) results in a poor sensitivity (45%) and a 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.\textsuperscript{103}

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]\textsuperscript{103} All patients 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 \( \geq 90 \text{ mmHg} \) 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 x 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 LRs were 3.83 (1.05 to 13.95) and 0.77 (0.48 to 1.24) respectively. The sensitivity, specificity, positive and negative LRs for a platelet count below 200 x 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 400 \( \mu \text{mol/l} \) 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 LRs for uric acid levels above 350 \( \mu \text{mol/l} \) 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 x 10\(^9\)/l, the sensitivity for platelet count was very poor (29\%), while specificity was very high (94\%). Using a threshold of 200 x 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 400 \( \mu \text{mol/l} \) and 350 \( \mu \text{mol/l} \) thresholds.

**Urea and serum creatinine**

Anumba et al.\textsuperscript{102} [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 significant LRs (LR+ 1.23, 1.0-1.5; LR- 0.76, 0.6-1.0).

**Liver function tests**

Anumba et al.\textsuperscript{102} [EL II] showed that in women suspected of having gestational hypertension alanine transaminase measure was not a significant predictor of pre-eclampsia.

No evidence was found for coagulation and clotting tests.

**Blood pressure**

Anumba et al.\textsuperscript{102} [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 LRs (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 LRs (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 LRs (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 LRs (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 significant LRs. Diastolic blood pressure had a sensitivity of 45-89%, specificity of 24-80% and significant LRs.

**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 PET, 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. 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 al 102 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.

In spite of this poor evidence base the GDG felt that the current use of investigations should be rationalised rather than entirely discontinued. 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.

6.4 Treatment of hypertension

Clinical effectiveness

Although there is a systematic review on the treatment of hypertension during pregnancy\textsuperscript{104}, 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.

Studies of gestational hypertension only

Alpha- and beta-blockers

Two trials [EL=1-] published in four articles investigated the effectiveness of labetalol versus placebo\textsuperscript{105-108}. In one trial, no statistically significant results were found for any of the maternal and fetal outcomes\textsuperscript{105;106}, whereas the other trial\textsuperscript{107;108} showed that fewer women receiving labetalol developed severe hypertension compared to women receiving a placebo (RR=0.35; 0.14 to 0.92).

No statistically significant results were found when these two studies were combined in the meta-analysis (see Table 6.1).

Two studies investigated the effectiveness of beta-blocker compared with placebo.\textsuperscript{109;110}[EL=1-] One study\textsuperscript{109} 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 study\textsuperscript{110} 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).\textsuperscript{111}[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**

A randomised control trial of low quality compared early treatment with methyldopa (before 28 weeks) versus no specific treatment or late treatment (after 28 weeks gestation). 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 ± 13 and late treated 272 days ± 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. 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 the not or late treated women (RR=0.31; 95% CI 0.17 to 0.58).

**Hydralazine and other treatments**

One low quality study compared metoprolol in combination with hydralazine with no treatment. No statistically significant results were obtained in this study (Table 6.1).

Another very small low quality study 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 6.1).

**Alpha- and beta-blockers**

Two low quality studies investigated labetalol versus methyldopa and one study compared labetalol versus hydralazine. No statistically significant results were reported for any of these three studies (Table 6.2).

**Beta-blockers and placebo**

Two studies compared beta-blockers with placebo. The study which investigated the beta-blocker metoprolol did not show any statistically significant results. The other study 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. The only outcome of interest reported was severe hypertension which failed to reach statistical significance (Table 6.2).

**Beta blockers and methyldopa**

Five studies 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 6.1).

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 randomized control trial conducted in France compared the effectiveness of nicardipine with metoprolol. 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 ≥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 nicardipine 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 6.1).

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**

A clinical trial conducted in Sri Lanka compared the effectiveness of nifedipine with methyldopa. A total of 126 women were included. The inclusion criteria were systolic blood pressure ≥ 140 mmHg, a diastolic blood pressure of ≥ 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.
## Table 6.1 Results for women with gestational hypertension (reported as RRs or ORs with 95% CIs)

<table>
<thead>
<tr>
<th>Study [Evidence Levels]</th>
<th>Severe hypertension</th>
<th>Pre-eclampsia/Proteinuria</th>
<th>Eclampsia/HELLP</th>
<th>Maternal death</th>
<th>Admission to HDU/ITU</th>
<th>Perinatal mortality</th>
<th>Small-for-gestational age</th>
<th>Preterm birth</th>
<th>Admission to neonatal unit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Labetalol versus placebo</strong></td>
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<tr>
<td>Pickles 105, 106 1992 [EL=1-]</td>
<td>5/70 versus 15/75 1992 [EL=1-]</td>
<td>17/70 versus 24/74 RR=0.75 (0.44 to 1.27)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/70 versus 0/74 not estimable</td>
<td>10/70 versus 5/74 RR=2.11 (0.76 to 5.88)</td>
<td>12/70 versus 17/74 RR=0.75 (0.38 to 1.45)</td>
<td>10/70 versus 9/74 RR=1.17 (0.51 to 2.72)</td>
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<tr>
<td>Cruickshank 108 1992 [EL=1-]</td>
<td>-</td>
<td>13/51 versus 17/63 RR=0.94 (0.51 to 1.76)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/51 versus 2/63 RR=0.25 (0.01 to 5.02)</td>
<td>6/51 versus 5/63 RR=1.48 (0.48 to 4.58)</td>
<td>10/51 versus 13/63 RR=0.95 (0.45 to 1.99)</td>
<td>18/51 versus 17/63 RR=1.31 (0.79 to 2.00)</td>
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<tr>
<td><strong>Labetalol versus methyldopa</strong></td>
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<tr>
<td>El-Qarmalawi 111 1994 [EL=1-]</td>
<td>1/54 versus 3/50 RR=0.31 (0.03 to 2.87)*</td>
<td>0/54 versus 10/50 RR=0.04 (0.003 to 0.73)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3/54 versus 3/50 RR=0.93 (0.20 to 4.38)*</td>
<td>(mean ± SD)</td>
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<tr>
<td><strong>Beta-blocker versus placebo</strong></td>
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<tr>
<td>Rubin 110 1983 (Atenolol) [EL=1-]</td>
<td>2/60 versus 7/60 RR=0.29 (0.06 to 1.32)</td>
<td>13/60 versus 21/60 RR=0.62 (0.34 to 1.12)</td>
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<td>-</td>
<td>16/46 versus 3/39 RR=0.41 (0.27 to 0.62)</td>
<td>1/6- versus 2/60 RR=0.49 (0.04 to 5.57)</td>
<td>9/59 versus 8/58 RR=1.11 (0.46 to 2.67)</td>
<td>9/59 versus 8/58 RR=1.11 (0.46 to 2.67)</td>
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<tr>
<td>Plouin 110 1990 (Oxprenolol) [EL=1-]</td>
<td>5/78 versus 11/76 RR=0.44 (0.16 to 1.21)</td>
<td>7/78 versus 7/72 RR=0.92 (0.34 to 2.50)</td>
<td>0/78 versus 0/76 not estimable</td>
<td>1/78 versus 0/76 RR=2.92 (0.13 to 70.68)</td>
<td>48/78 versus 46/76 RR=1.02 (0.79 to 1.31)</td>
<td>2/78 versus 3/76 RR=0.64 (0.10 to 3.94)</td>
<td>7/78 versus 9/76 RR=1.11 (0.46 to 2.67)</td>
<td>11/78 versus 14/76 RR=0.77 (0.37 to 1.58)</td>
<td>16/76 versus 24/75 RR=0.66 (0.38 to 1.14)</td>
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<td><strong>Platelets versus placebo</strong></td>
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<td>Schiff 111 1990 (Aspirin) [EL=1+]</td>
<td>-</td>
<td>6/23 versus 6/24 RR=1.04 (0.39 to 2.77)</td>
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<tr>
<td><strong>Bed-rest versus normal activities at home</strong></td>
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<tr>
<td>Crowther 86 1992 [EL=1+]</td>
<td>22/95 versus 3/90 OR=0.52 (0.27 to 0.99)</td>
<td>58/95 versus 56/90 OR=0.91 (0.53 to 1.72)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>12/95 versus 14/90 OR=0.78 (0.34 to 1.80)</td>
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</tbody>
</table>
a Caesarean section due to uncontrolled blood pressure as a proxy
b Preterm labour

The results from mixed studies give other information but are very varied in their conduct and their recruitment (see Table 6.2).
Table 6.2 Results for the mixed population (reported as RRs or ORs with 95% CIs)

<table>
<thead>
<tr>
<th>Study [Evidence Levels]</th>
<th>Severe hypertension</th>
<th>Pre-eclampsia/proteinuria</th>
<th>Eclampsia/HELLP</th>
<th>Maternal death</th>
<th>Admission to HDU/ITU</th>
<th>Perinatal mortality</th>
<th>Small-for-gestational age</th>
<th>Preterm birth</th>
<th>Admission to neonatal unit</th>
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<tbody>
<tr>
<td><strong>Labetalol versus methyldopa</strong></td>
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<tr>
<td>Lamming [EL=1] 1980</td>
<td>0/14 versus 2/12 (0.01 to 3.29)</td>
<td>5/14 versus 9/12 (0.22 to 1.03)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/14 versus 0/12 not estimable</td>
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</tr>
<tr>
<td>Plouin [EL=1] 1988</td>
<td>8/91 versus 8/85 (0.37 to 2.38)</td>
<td>44/91 versus 46/85 (0.67 to 1.19)</td>
<td>1/91 versus 4/85 (0.03 to 2.05)</td>
<td>11/91 versus 12/81 (0.38 to 1.75)</td>
<td>22/91 versus 21/81 (0.58 to 1.65)</td>
<td>34/91 versus 29/81 (0.70 to 1.55)</td>
<td>-</td>
<td>19/39 versus 16/35 (0.66 to 1.73)</td>
<td></td>
</tr>
<tr>
<td>Redman [EL=1] 1978</td>
<td>-</td>
<td>19/39 versus 10/35 (0.92 to 3.15)</td>
<td>-</td>
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<tr>
<td><strong>Labetalol versus hydralazine</strong></td>
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<tr>
<td>Hjertberg [EL=1] 1993</td>
<td>9/9 versus 7/11 (0.96 to 2.41)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/9 versus 1/11 (0.02 to 8.78)</td>
<td>3/9 versus 8/11 (0.17 to 1.24)</td>
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<tr>
<td><strong>Beta-blocker versus placebo</strong></td>
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<tr>
<td>Wichman [EL=1] 1984 (Metoprolol)</td>
<td>1/26 versus 0/26 (0.13 to 70.42)</td>
<td>11/26 versus 11/26 (0.53 to 1.89)</td>
<td>-</td>
<td>-</td>
<td>0/26 versus 0/26 not estimable</td>
<td>16/26 versus 19/26 (0.57 to 1.24)</td>
<td>0/26 versus 1/26 (0.39 to 7.03)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bott-Kanner [EL=1] 1992 (pindolol)</td>
<td>6/30 versus 15/30 (0.18 to 0.89)</td>
<td>2/30 versus 5/30 (0.08 to 1.90)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1/30 versus 0/30 (0.30 to 7.03)</td>
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<tr>
<td>Study</td>
<td>Beta-blocker versus methyldopa</td>
<td>Beta-blocker versus nicardipine</td>
<td>Metroprolol plus hydralazine versus no treatment</td>
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<tr>
<td>Fidler 1983 (Oxprenolol) [EL=1-]</td>
<td>7/50 versus 7/50 RR=1.00 (0.38 to 2.64)</td>
<td>15/50 versus 7/50 RR=2.14 (0.96 to 4.80)</td>
<td>10/86 versus 6/82 RR=1.59 (0.60 to 4.17)</td>
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<tr>
<td>Gallery 1979 (Oxprenolol) [EL=1-]</td>
<td>10/96 versus 10/97 RR=0.91 (0.40 to 2.07)</td>
<td>8/50 versus 3/50 RR=2.67 (0.75 to 9.47)</td>
<td>3/86 versus 1/82 RR=2.93 (0.30 to 28.73)</td>
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<tr>
<td>Oumachigui 1992 (Metoprolol) [EL=1-]</td>
<td>1/16 versus 0/14 RR=0.31 (0.04 to 2.68)</td>
<td>1/16 versus 1/16 RR=1.00 (0.07 to 14.64)</td>
<td>6/83 versus 4/81 RR=1.46 (0.43 to 5.00)</td>
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<tr>
<td>Livingstone 1983 (Propranolol) [EL=1-]</td>
<td>6/14 versus 4/14 RR=1.50 (0.54 to 4.18)</td>
<td>-</td>
<td>23/83 versus 20/81 RR=1.12 (0.67 to 2.00)</td>
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<tr>
<td>Ellenbogen 1986 (Pindolol) [EL=1-]</td>
<td>0/16 versus 0/16 not estimable</td>
<td>0/16 versus 0/16 not estimable</td>
<td>-</td>
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<tr>
<td>Jannet 1994 (Metoprolol) [EL=1-]</td>
<td>8/50 versus 3/50 RR=2.67 (0.75 to 9.47)</td>
<td>-</td>
<td>3/86 versus 1/82 RR=2.93 (0.30 to 28.73)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Högestedt 1985 [EL=1-]</td>
<td>10/86 versus 6/82 RR=1.59 (0.60 to 4.17)</td>
<td>-</td>
<td>6/83 versus 4/81 RR=1.46 (0.43 to 5.00)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Beta-blocker versus beta-blocker

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuimala 1988 (Atenolol versus Pindolol)</td>
<td>3/24 vs 4/27</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR = 0.84 (0.21 – 3.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Hydralazine versus hydralazine plus propranolol or pindolol

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>RR 0/36 vs 0/15</th>
<th>RR 0/15 vs 0/15</th>
<th>RR 36/36 vs 15/15</th>
<th>RR 15/15 vs 15/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paran 1995 (EL=1)</td>
<td>0/36 vs 0/15</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>0/15 vs 0/15</td>
<td>not estimable</td>
<td>not estimable</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>13/36 vs 0/15</td>
<td>RR = 1.35 (0.53 to 3.48)</td>
<td>not estimable</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>10/36 vs 0/15</td>
<td>RR = 1.39 (0.44 to 4.35)</td>
<td>not estimable</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Calcium-channel blocker verapamil versus beta-blocker

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>RR 0/22 vs 0/22</th>
<th>RR 0/22 vs 0/22</th>
<th>RR 0/25 vs 0/25</th>
<th>RR 0/25 vs 0/25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marlettini 1990 (Pindolol)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>EL=1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Marlettini 1990 (Atenolol)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>EL=1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Calcium-channel blocker versus methyldopa

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>RR 40/63 vs 24/63</th>
<th>RR 1/63 vs 1/63</th>
<th>RR 1/63 vs 1/63</th>
<th>RR 1/63 vs 1/63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaryawardana 1994 (Nifedipine)</td>
<td>40/63 vs 24/63</td>
<td>-</td>
<td>1/63 vs 1/63</td>
<td>RR = 1.67</td>
<td>(1.16 to 2.40)</td>
</tr>
<tr>
<td></td>
<td>EL=1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Methyldopa versus no specific treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>RR 1/63 vs 1/63</th>
<th>RR 1/63 vs 1/63</th>
<th>RR 1/63 vs 1/63</th>
<th>RR 1/63 vs 1/63</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redman 1976</td>
<td>-</td>
<td>Not significant</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>EL=1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

---

1. The outcome reported was need for treatment for acute hypertension
2. The outcome reported was HELLP syndrome
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 \textsuperscript{62,105-111,130} 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 \textsuperscript{[EL=1-]} investigated the effectiveness of alpha- and beta-blockers. One study\textsuperscript{111} found labetalol to lower the incidence of severe hypertension compared to placebo, whereas another\textsuperscript{109} found beta-blocker to lower the rate of hospital admission before birth compared to placebo. One quasi-randomised study\textsuperscript{130} found labetalol to lower the incidence of pre-eclampsia compared to methyldopa.

Overall, 19 studies \textsuperscript{[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 nicardipin and one study with another beta-blocker. One study compared metropolol 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 3.3

Anti-platelet agents

Low-dose aspirin

A randomized control trial on the effectiveness of low-dose aspirin in gestational hypertension was conducted in Israel\textsuperscript{130}[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 renal disorder, or antihypertensive treatment before admission were excluded. 23 women were randomly allocated to receive 100mg acetylsalicylic acid 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 statistical significant differences between the treatment and the placebo group were found for moderate to severe pre-eclampsia, gestational age at delivery, newborn weight, newborn percentile, and 5 minute Apgar score.

**Rest/bed-rest**

A randomized control trial was conducted in Zimbabwe to compare the effectiveness of hospital admission for bed rest with continuation of normal activities at home. 62 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 $\geq 100$ 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 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 women with gestational hypertension. However no statistically significant differences were found for women following bed rest and those who continued normal activities at home for the other outcomes – the mean length of hospital stay, gestational age at delivery, preterm delivery <34 weeks, development of proteinuria or severe proteinuria, incidence of small-for-gestational age infants and admission to a neonatal unit.

**Evidence statement**

A well conducted RCT found bed rest compared to normal activities at home to be effective in preventing severe hypertension.

**GDG interpretation of the evidence**

Limited good quality evidence is available in relation to women with gestational hypertension. There is no evidence that blood pressure lowering treatment for mild to moderate gestational hypertension 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 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/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 evidence on bed rest was in an unrepresentative health care setting which is not applicable to the UK. The GDG does not consider the
evidence on aspirin supports its commencement in gestational hypertension.

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.

**Recommendations**

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

In women with gestational hypertension, take account of the following risk factors when planning assessment and follow-up:

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

Manage gestational hypertension as described in the table below:

<table>
<thead>
<tr>
<th>Degree of hypertension</th>
<th>Mild hypertension (&lt;149/99 mmHg)</th>
<th>Moderate hypertension (150/100 to 159/109 mmHg)</th>
<th>Severe hypertension (160/110 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit to hospital</td>
<td>No</td>
<td>Yes - with oral labetalol to keep:</td>
<td>Yes - with oral labetalol to keep:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• diastolic blood pressure less than 100 mm Hg</td>
<td>• diastolic blood pressure less than 100 mm Hg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• systolic blood pressure less than 150 mm Hg</td>
<td>• systolic blood pressure less than 150 mm Hg</td>
</tr>
<tr>
<td>Treat</td>
<td>No</td>
<td>Yes at least twice a week</td>
<td>Yes at least four times a day</td>
</tr>
<tr>
<td>Measure blood pressure</td>
<td>Yes rout. not more than once a week</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Test for proteinuria</td>
<td>Yes at each visit using automated dipsticks</td>
<td>Yes at each visit using automated dipsticks</td>
<td>Yes daily using automated dipsticks</td>
</tr>
</tbody>
</table>

32 Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.
Blood tests

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(none in addition to those for routine antenatal care)</td>
<td>test urea electrolytes and request a full blood count, platelets, serum creatinine, transaminases, bilirubin do not carry out further blood tests if no proteinuria at subsequent visits.</td>
</tr>
<tr>
<td></td>
<td>test at presentation: full blood count, platelets, serum creatinine, transaminases, bilirubin monitor weekly: full blood count, platelets, serum creatinine, transaminases, bilirubin</td>
</tr>
</tbody>
</table>

In women receiving outpatient treatment for severe gestational hypertension, 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.

In women with gestational hypertension, offer alternative antihypertensive treatment after considering side-effect profiles for the woman, fetus and neonate.

Do not use bed rest as a treatment for gestational hypertension.

**Research recommendations**

What is the role of the assessment of biochemical or haematological parameters at diagnosis of new hypertension in pregnancy and during surveillance of new hypertension?

Why this is important

Pre-eclampsia is a multisystem disorder, but it is not clear whether routine assessment of a range of biochemical or haematological parameters aids 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 that examine a range of parameters singly and serially (renal function, liver function, coagulation, measurement of proteinuria) in women with new 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 devised 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.

**6.5 Fetal monitoring**

**Clinical effectiveness**

See Chapter 8
**GDG interpretation of the evidence**

There are no studies that examine fetal surveillance in a population that only includes women with gestational hypertension and therefore inference on surveillance 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 this 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.

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 5).

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

### 6.6 Timing of birth

**Clinical effectiveness**

One multicentre, open-label RCT[^131:241] [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 (n=756) women with gestational hypertension or mild pre-eclampsia. Women were randomly allocated, using a blocked randomisation with a variable block size between 2 and 8, into an induction of labour (n= 377) or an expectant monitoring (n= 379) group.
Randomisation was stratified by centre, parity and hypertensive related disease. Baseline characteristics of the two groups were similar.

No maternal or neonatal death occurred in either of the groups. There was a significantly lower risk of severe hypertension in the induction of labour group (measured by sBP: 55/377 versus 88/379: RR 0.61, 95% CI 0.46-0.81; measured by dBP: 62/377 versus 103/379: RR=0.61, 95% CI 0.46-0.81). Women in the induction of labour group were also less likely to develop adverse maternal outcomes (117/377 versus 166/379: RR 0.71: 95% CI 0.59-0.86). There was a trend toward less admission to ICU in the induction of labour group. However, this difference did not reach statistical significant level (6/377 versus 14/379: 95% CI 0.16-1.07). As for neonatal outcomes, no significant differences were found between the two groups, including adverse neonatal outcomes, admission to ICU, high care or medium care level and the length of stay in these units. There were no differences in method of delivery (spontaneous, vaginal instrumental or caesarean section) between the two groups.

Evidence statement

One RCT\textsuperscript{241} [EL 1+] showed that in women with gestational hypertension or mild pre-eclampsia, women undergoing induction of labour were at significantly lower risk of developing severe hypertension, or adverse maternal outcomes than those managed expectantly. No differences were found in neonatal outcomes or methods of delivery.

Cost effectiveness

A literature search did not retrieve any published economic evaluation comparing an immediate birth strategy with expectant management strategy in women with mild to moderate gestational hypertension at term. The two policies have different resource implications and health consequences for mother and baby. In view of the lack of published cost-effectiveness evidence the GDG requested a de novo economic analysis to help in its guideline recommendations. The results of this analysis are summarised here, but further details can be found in Appendix K.

Using the recently published data from the HYPITAT trial,\textsuperscript{241} we constructed a decision tree in both Excel\textsuperscript{™} and TreeAge Pro\textsuperscript{®} to estimate the cost-effectiveness of the two strategies. Our model demonstrated that immediate birth strategy compared to expectant management strategy in women with mild to moderate gestational hypertension at term is cost saving. Immediate birth dominates expectant management in that it results in better maternal outcomes and is less costly when compared with expectant management. The mean cost per patient for the immediate birth strategy was estimated to be £2,774 compared to £2,990 for expectant management. This resulted in savings of £215 per patient as well as generating 0.04 more QALYs. We tested the robustness of the base results using univariate sensitivity analysis and this did not affect the base case conclusions.

GDG interpretation of the evidence

The HYPITAT study\textsuperscript{241} combined mild pre-eclampsia, as defined in this guideline, and mild gestational hypertension, defined differently: above 95 mmHg compared with above 90 mmHg in this guideline. Subgroup data are available for the primary outcome and for caesarean section. The overall maternal benefits seen 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. The subgroup analysis for gestational hypertension shows a trend to better maternal...
outcomes but the CI crosses unity. In addition women with mild
gestational hypertension with blood pressures between 90 and 94 mmHg
were not studied. The GDG feels on this basis that there is no evidence
that changes the current conservative management for gestational
hypertension at diastolic blood pressures of less than 95 mmHg.
Management is less clear when the blood pressure is above 95 mmHg
without proteinuria. There appear to be no disadvantages to immediate
birth, in terms of increased caesarean section or adverse neonatal
outcome but progression to severe disease will be avoided. The health
economic analysis favours birth after 37 weeks when the diastolic blood
pressure is over 95 mmHg.

**Recommendations**

For women with gestational hypertension whose blood pressure is lower
than 159/109 mmHg with or without antihypertensive treatment, do not
offer birth before 37 weeks.

For women with refractory severe gestational hypertension, offer birth
before 37 weeks after a course of antenatal steroids has been completed.

Offer birth to women with gestational hypertension whose diastolic blood
pressure is greater than 95 mmHg with or without antihypertensive
treatment after 37 + 0 weeks.

Offer birth to women with gestational hypertension after 39 + 0 weeks.

### 6.7 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 1-132 compared the use of timolol and
methyldopa in the management of puerperal hypertension. Untreated
postpartum patients 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 evidence identified in relation to antihypertensive drugs and breastfeeding is presented in Table 4.4.

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 to 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 effectiveness of postnatal drug use and efficacy in women who have had gestational hypertension and therefore the GDG’s view is 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.

The GDG is aware that the recent MHRA newsletter (May 2009 issue of the MHRA Drug Safety Update, available at http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON046451) suggests the preferential use of methyldopa in breastfeeding women. However, there is very little good evidence on drugs and breastfeeding, particularly for clinical outcomes, and the antihypertensive drugs likely to be used in women with gestational hypertension (labetalol, nifedipine, methyldopa) appear to be safe. The priority is to ensure effective blood pressure control and wellbeing in the woman and to reinforce general advice to encourage and support breastfeeding.

Women with gestational hypertension who have received 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 discharge from hospital. There should be a formal medical review for women who have had gestational hypertension at the normal (6-8 week) postnatal visit.

Recommendations

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

- daily while the woman is an inpatient
- between day 3 and day 5 after birth
- as clinically indicated if antihypertensive treatment is changed after birth.

In women with gestational hypertension who have recently given birth, aim to keep blood pressure below 140/90 mmHg.

In women with gestational hypertension who have just given birth, continue use of antenatal antihypertensive treatment.
If a woman has received methyldopa to treat gestational hypertension, stop within 2 days of birth.

For women with gestational hypertension who have recently 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.

For women who did not receive antihypertensive treatment and have recently given birth, start antihypertensive treatment if their blood pressure exceeds 150/100 mmHg.

For women with gestational hypertension who have recently given birth and are being discharged from hospital write a care plan that includes all of the following:

- frequency of blood pressure monitoring required
- thresholds for reducing or stopping treatment
- indications for early referral to primary care for blood pressure review.

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

Refer women who have had gestational hypertension and who still require antihypertensive treatment at the postnatal visit (6–8 weeks after the birth) for specialist assessment.

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Methyldopa is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.
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 review investigated the precise estimates of 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 LRs for stillbirth (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) found significant LRs for small for gestational age (2+ one study, n= 307, LR+ 1.3, 1.2-2.1, LR- 0.69, 0.59-0.82; 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 were found at a 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 significant LRs for NICU admission (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 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 positive LR for eclampsia (10g/24hr; LR+ 2.7, 1.1-6.2). However, no significant negative LR was found at the same cut off, 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 positive LR for perinatal death (500 mg/mmol; LR+ 5.3, 1.3-22.1). However, no significant negative LR 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 LR for placental abruption (3 studies, n= 247), HELLP syndrome (4 studies, n= 558) or neonatal death (5 studies, n= 698). 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] 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 μmol/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% CI 0.56 to 1.4) respectively, and 1.9 (95% CI 0.85 to 4.2) and 0.92 (95% CI 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 non 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. 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 insulin dependent diabetes mellitus. Pre eclampsia was defined as blood pressure ≥140/90 mmHg together with albuminuria of at least 300mg/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, lactic
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 <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 alanine amino transferase (ALAT) represented a change of 0.1 μkat/l. Maternal complications were defined as eclampsia, placental abruption, and oliguria (urine production <600ml/24hours), and HELLP syndrome (LDH>8 μkat/l, alanine amino-transferase (ALAT) >0.70, and platelet count <150x10^9/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 patients 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, alanine aminotransferase (ALAT), 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 alanine aminotransferase (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 study [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 hyperuricemia (n= 116), HELP 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 10^9/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= 0.068 respectively), creatinine greater than 110 μM (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 anemia (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, alanine aminotransferase, 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 alanine aminotransferase were associated with referral to neonatal intensive care unit.

A case-control study showed an association between a platelet count less than 100 x 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 >100x10^9/l.
7.5 Treatment of hypertension

Clinical effectiveness

The data are summarised in Table 6.1 and the details of the studies outlined.

Methyldopa

Two trials investigated the effectiveness of methyldopa, one study\textsuperscript{137} compared it with no treatment and one with the calcium-channel blocker isradipine\textsuperscript{138}. Both studies are of evidence level [EL=1-].

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

A randomized control trial conducted in Sudan compared methyldopa with no drug treatment.\textsuperscript{137}[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 randomised control trial was conducted in Singapore comparing methyldopa with isradipine.\textsuperscript{138}[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 patients were excluded after randomisation. No further information on randomisation was given and none of the participants 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.

Alpha- and beta-blockers

One well conducted randomised control trial investigated the effectiveness of labetalol versus no treatment.\textsuperscript{109}[EL=1+]. 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 results were found for any of the other maternal or fetal outcomes.
Calcium-channel blockers

A well conducted USA randomised control trial compared nifedipine in combination with bed-rest with bed rest alone. 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 quality found methyldopa effective in preventing proteinuria compared to placebo. Another small trial of low quality compared methyldopa with isradipine but did not achieve any statistically significant results. One well conducted RCT found labetalol reduced the incidence of severe hypertension compared to placebo. A well conducted trial 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

Limited good quality evidence is available in relation to women with pre-eclampsia. There is no evidence that blood pressure lowering treatment for mild to 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. 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 labetralol reduces the risk of 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.
Recommendations

Assess women with pre-eclampsia at each consultation; assessment should be performed by an appropriately trained healthcare professional.

Manage pre-eclampsia as described in the table below:

<table>
<thead>
<tr>
<th>Degree of hypertension</th>
<th>Mild hypertension (&lt;149/99 mmHg)</th>
<th>Moderate hypertension (150/100 to 159/109 mmHg)</th>
<th>Severe hypertension (160/110 mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit to hospital</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Treat</td>
<td>No</td>
<td>with oral labetalol(^\text{34}) to keep</td>
<td>with oral labetalol(^\text{34}) to keep</td>
</tr>
<tr>
<td></td>
<td>(none in addition to routine</td>
<td>• diastolic blood pressure less than 100 mm Hg</td>
<td>• diastolic blood pressure</td>
</tr>
<tr>
<td></td>
<td>antenatal care)</td>
<td>but more than 80 mm Hg</td>
<td>less than 100 mm Hg but</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• systolic blood pressure less than 150 mm Hg</td>
<td>more than 80 mm Hg</td>
</tr>
<tr>
<td>Measure blood pressure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>At least four times a day.</td>
<td>At least four times a day.</td>
<td>More frequently than six hourly,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>depending on clinical circumstances.</td>
</tr>
<tr>
<td>Test for proteinuria</td>
<td>Do not repeat quantification of</td>
<td>Do not repeat quantification of</td>
<td>Do not repeat quantification of</td>
</tr>
<tr>
<td></td>
<td>proteinuria</td>
<td>proteinuria</td>
<td>proteinuria</td>
</tr>
<tr>
<td>Blood tests</td>
<td>Monitor using the following</td>
<td>Monitor using the following</td>
<td>Monitor using the following</td>
</tr>
<tr>
<td></td>
<td>tests twice a week: full blood</td>
<td>tests three times a week: full</td>
<td>tests every other day: full</td>
</tr>
<tr>
<td></td>
<td>count, platelets, serum</td>
<td>blood count, platelets, serum</td>
<td>blood count, platelets, serum</td>
</tr>
<tr>
<td></td>
<td>creatinine, transaminases,</td>
<td>creatinine, transaminases,</td>
<td>creatinine, transaminases,</td>
</tr>
<tr>
<td></td>
<td>bilirubin.</td>
<td>bilirubin.</td>
<td>bilirubin.</td>
</tr>
</tbody>
</table>

7.6 Fetal monitoring

Clinical effectiveness

The main evidence is presented in Section 6. Only computerised cardiotocography is studied specifically in severe pre-eclampsia and is presented here.

Routine versus computerised cardiotocography in severe pre-eclampsia

One RCT\(^ {140} \) [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. Patients 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, \(^ {34}\) Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.
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

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
cardiocography 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

Policy of expectant management or immediate birth

Two high quality RCTs [EL=1++ 141, EL=1+ 142] investigated whether early
delivery or expectant management of severe pre-eclampsia in
pregnancies ≤ 34 weeks is more beneficial to maternal and neonatal
outcome. In both trials, women had a 24 to 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 group were delivered when they reached 34 weeks.

Earlier delivery in this expectant group was implemented if either the
maternal or fetal condition deteriorated.

The larger of these two RCTs is from the USA [EL=1++] 141 and involves 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-existent
medical problems were excluded. Women were randomly assigned by
computer-generated random numbers to either early delivery or
expectant management. The mean age of participants (22 ± 4 yrs early
delivery, 23± 6 yrs expectant, NS), and the mean blood pressure (170/110
± 10/5 mmHg early delivery; 172/112 ± 9/4 mmHg expectant, NS) at the
start of the study were similar between the two groups. Early delivery
patients (n=46) were prepared for delivery, either by caesarean or
induction, 48 hours after glucocorticoids were administered. Expectant
management patients (n=49) were managed with bed rest, oral
antihypertensives, and intensive antenatal fetal testing. Gestational age
at delivery was significantly different between the two groups (early
delivery 30.8 ± 1.7 wks, expectant 32.9 ± 1.5 wks, 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). Incidences of abruptio placenta and HELLP syndrome were similar in the two groups and no eclampsia or perinatal death was reported in either group.

The other RCT was conducted in South Africa [EL=1+] 142. It included 38 women at 28-34 weeks with severe pre-eclampsia who were randomly assigned to either early delivery (n=20) or expectant management (n=18). The process of randomization was not described adequately. There was no difference between the mean age of participants (23 ± 5 yrs early delivery, 23± 3 yrs expectant, NS), and the mean blood pressure at the time of entry in the study (159/107 ± 18/8 mmHg early delivery; 159/108 ± 19/11 mmHg expectant, NS). Gestational age at delivery was significantly different between the two groups (early delivery 211 ± 15 days, expectant 223 ±13 days, p <0.05). Expectant management was not associated with an increase in maternal complications (cesarean sections, placental abruption), nor was it associated with an increase in the 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).

Where applicable, we performed meta-analysis of the evidence presented in these two RCTs. Neonates in the early delivery group showed increase frequency of hyaline membrane disease (2RCTs, N=133, RR=2.30, 95% CI 1.39 to 3.81) and necrotising enterocolitis (2RCTs, N=133, RR=5.54, 95% CI 1.04 to 29.56) than those in the expectant group, but no statistically significant difference was observed for stillbirth or death after delivery (2RCTs, N=133, RR=1.50, 95% CI 0.42 to 5.41). Meta-analysis of maternal complications (placental abruption, and cesarean sections) gave no significant differences between the two groups. Other outcomes were only reported by either of the studies.

One high quality trial compared immediate birth with expectant management in mild and moderate pre-eclampsia after 36 weeks (ref). The evidence statement is presented in Section 4.

**Effect of fetal growth restriction**

A randomised control multi-centred study (GRIT) 143 was undertaken in 13 European countries including the UK between 1993 and 2001 to assess the effect of immediate delivery compared with delayed delivery in pregnancies (singletons and multiples) 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 group and 274 in the delayed group - the incidence of hypertension was 46% and 40% respectively. Outcomes for the hypertensive cases were not separately available. Overall perinatal loss was similar between the groups (10% and 9% respectively) - there were 2 stillbirths in the immediate groups and 9 in the delayed group but 23 neonatal deaths in the immediate group and 12 in the delayed group. [EL=1+] 144

A second study undertook a 2 year review of babies born under the GRIT protocol 144. There were 290 babies in the immediate group and 283 in the delayed group - death or disability occurred in 55 and 44 respectively a non-significant difference OR 1.1 (CI 0.7-1.8). Most of the observed
disability was in babies born before 31 weeks (13% immediate and 5% delayed), and this was a non significant difference. [EL=1+]

A retrospective Canadian cohort study \(^{145}\) assessed morbidity and mortality rates for both mother and fetus in severe pre-eclampsia when managed expectantly. Women whose condition was too unstable and who required immediate 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 magnesium sulphate, betamethasone and antihypertensives were used to stabilise them. Those who became stable started expectant management including bed rest, maternal monitoring, oral anti-hypertensives, and fetal assessment with ultrasonography and, when available, Doppler. 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 < 10th 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 significant differences were found with respect to renal insufficiency, pulmonary oedema, eclampsia, and placental abruption. Similarly, no 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 ≤ or > 5th percentile, gestational age appeared to be the best predictor of good neonatal outcomes and after 30 weeks, the incidence of neonatal complications decreased by two-thirds. [EL=2+].

A retrospective population study undertaken in the Trent region \(^{146}\), UK 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. The Tables have been reproduced with the authors’ permission. [EL=2+]

A prospective cohort study from the USA\(^{147}\) [EL=2++] looked at the likelihood of survival, survival without profound neurodevelopmental impairment at a corrected age of 18 to 22 months in 4446 infants born at 22-25 weeks age. At 18-22 months, 49% of the study infants had died, 61% had died or had profound impairment, and 73% had died or had impairment. The rates for these outcomes according to the week of gestation were 95%, 98% and 99% respectively among study infants born at 22 weeks; 74%, 84% and 91% among study infants born at 23 weeks, 44%, 57% and 72% among study infants born at 24 weeks, and 25%, 38% and 54% among study infants born at 25 weeks.

**HELLP syndrome**

Dutch retrospective cohort study \(^{148}\) 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 HELLP women. 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 (≤2-day difference).

There was no 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). Patients 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 of the interval between admission and delivery was 3 days (0-59) in the HELLP group, and 9 (0-63) in the group without HELLP. No maternal mortality, pulmonary oedema or renal insufficiency cases were found. Incidence of eclampsia and placental abruption was not significantly different between the two groups. Similarly, no differences were found 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 a statistically significant influence from gestation age (RR=1.4, 95% CI 1.1 to 1.7 week gestational age) and antihypertensive treatment (RR=3.6, 95% CI 1.02 to 12.4). [EL=2+].

Cost effectiveness

The literature search did not retrieve any published economic evaluation comparing immediate birth strategy with expectant management strategy in women with mild to moderate pre-eclampsia pre-term (34-37 weeks gestation). In view of the lack of published cost-effectiveness evidence the GDG requested a de novo economic analysis to help in its guideline recommendations. The results of this analysis are summarised below but full details of the analysis are provided in Appendix L.

There are no published effectiveness trials comparing immediate birth with expectant management in women with mild/moderate PET 34-37 weeks. However for this model we used data from a retrospective case control study undertaken in the USA. The study was 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 assumed to be the same as outcomes reported at 35 weeks. The outcomes for expectant management were assumed to be those reported in week 36 and 37. We constructed a decision tree in both Excel™ and TreeAge Pro® to estimate the cost-effectiveness of the two strategies.

Our model demonstrated that immediate birth strategy compared to expectant management strategy in women with mild to moderate PET pre-term was cost-effective at the £20,000 per QALY threshold, with an estimated ICER of £2,900 per QALY. We tested the robustness of the base case results using univariate sensitivity analysis. The model results are sensitive to assumptions about incidence of severe disease used in the model. Overall the GDG is aware that this result needs to be interpreted with caution because of the lack of comparative data for the two policies. The GDG is aware of an on-going clinical trial (the Hypertension and Pre-eclampsia Intervention Trial in the Almost Term patient (HYPITAT-II) comparing the two policies; this open multi-centre trial is funded by the Netherlands Organisation for Health Research and Development and...
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 maternal outcomes in terms of the development of HELLP syndrome, placental abruption, need for caesarean section or eclampsia.

An RCT investigated the appropriate timing of delivery in pregnancies between 24 and 36 weeks when there was potential fetal compromise showed no difference in perinatal outcome overall 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. 2 year follow up likewise showed no difference in the rate of death and disability between the groups.

Another retrospective study [EL=2+] of the expectant management of severe pre-eclampsia prior to 34 weeks showed that neonatal outcome was related to the 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 results in similar maternal and perinatal outcome.

Health economic modelling suggests that immediate birth is cost-effective, though the GDG appreciate 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, though studies of expectant management excluded women with serious complications. With this caveat the GDG concluded that expectant management of severe pre-eclampsia/HELLP syndrome should be considered unless they are clear maternal or fetal indications for immediate birth. The GDG considered the lack of evidence of benefit in prolonging pregnancy beyond 34 weeks in severe pre-eclampsia justifies advising birth after this time.

Although fetal growth restriction is excluded from some of the studies of expectant care and there is evidence that in the preterm survival may be less in the small for gestation baby, the GDG felt that there were no strong grounds for birth before 34 weeks in women with pre-eclampsia simply on the basis of poor fetal growth.

Similarly the presence of the features of HELLP syndrome alone should not influence timing of birth.

There is no evidence concerning the consequences for mother and baby in conservative management of mild /moderate pre-eclampsia before 36 weeks but clear evidence of clinical benefit and cost effectiveness for immediate birth after this (Section 4.6)
The GDG feel that as a proportion of women in this group will progress to severe pre-eclampsia with its potential serious outcomes, an offer of immediate birth should be considered. The GDG appreciates that other factors, both maternal and fetal and availability of neonatal facilities may affect the precise timing.

Specific values of biochemical and haematological parameters, including the degree of proteinuria, are poor predictors of outcomes for both woman and baby, making it difficult to give guidance. In general the GDG felt that there were no grounds for recommending birth based on any absolute threshold. The disease process is different in individual women and there is interaction in clinical terms between maternal multisystem involvement, blood pressure and fetal status. The GDG felt that it was essential to ensure that a consultant/specialist review each individual case and that a care plan is developed to include the acceptable thresholds of all monitored variables for that pregnancy.

**Recommendations**

Manage pregnancy in women with pre-eclampsia conservatively until 34 weeks.

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

Consultant obstetric staff should write a plan for fetal monitoring.

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 haematological, biochemical or clinical indications develop as specified in the consultant plan
- fetal indications develop as specified in the consultant plan.

Advise birth for women with severe pre-eclampsia after 34 weeks once their blood pressure is controlled and, if appropriate, a course of antenatal steroids has been completed.

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.

Advise 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 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 infant would have costs.
Randomised controlled trials should be carried out that compare policies of immediate planned birth between 34 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+]\(^\text{150,151}\) and four had evidence level of [EL=1-]\(^\text{132,152-154}\).

Need for antihypertensive agents postnatally

A small RCT from the USA [EL 1-]\(^\text{152}\) investigated the efficacy of nifedipine in controlling hypertension and improving urine output in postpartum patients 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+]\(^\text{150}\) 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-]\(^\text{132}\) compared the use of timolol and methyldopa in the management of puerperal hypertension. Untreated postpartum
patients 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 patients 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+] 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+] investigated whether a brief postpartum course of Furosemide for patients with pre-eclampsia benefited recovery and shortened hospitalisation. Two hundred sixty-four patients 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 patients 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+] investigated diuretics use postnatally to lower blood pressure in women 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 EL1+ and other two with EL1-) suggest no beneficial effect of one drug over the other.

Antihypertensive drugs and breastfeeding

The evidence for this is presented in chapter 3.

Use of magnesium sulphate in the postpartum period

A cohort study from the USA 155[EL=2+] aimed to profile patients with hypertensive disorders of pregnancy who required re-institution of magnesium sulphate therapy for disease exacerbation. 503 women with hypertensive disorders during pregnancy were included (284 mild pre-eclampsia, 105 severe pre-eclampsia, 61 superimposed pre-eclampsia, 8 eclampsia, and 45 with HELLP syndrome). All patients received intravenous magnesium sulphate prophylaxis (4g then 2g/h) during the intrapartum period. Magnesium sulphate was re-instituted (for 24h) in patients with a sustained systolic blood pressure >160 mmHg and diastolic blood pressure >110 mmHg for at least 2 hours and with an associated headache or visual change. Of the 503 patients, 38 were re-instituted with MgSO4 (18 mild pre-eclampsia, 6 severe pre-eclampsia, 11 superimposed pre-eclampsia, 3 HELLP syndrome).

Maternal age, parity, maternal weight, admission creatinine level and route of delivery were not predictors of the need for magnesium sulphate re-institution. The gestational age of women requiring MgSO4 was significantly lower than those who did not (32.4 ± 4.2 weeks versus 36.3 ± 4.2, p < 0.001). Also, the re-instituted group had received their MgSO4 course for a longer duration in the antepartum period (19 hrs (2-54) versus 9 hrs (2-96), p < 0.001), and the postpartum period (6 hrs (2-77) versus 4 (92-72), p < 0.001), had higher postpartum mean arterial pressure (113.2 ± 11.2 versus 105.6 ± 11.3 mmHg, p < 0.001) and longer postpartum hospital stay (4.6 ± 1.7 versus 3.0 ± 1.3 days, p < 0.001). Multivariate analysis which adjusts for potential confounders identified only earlier gestational age at presentation and higher mean arterial pressure during the initial postpartum magnesium course as significant predictors of the need for magnesium sulphate re-institution.

The medial interval between the cessation of the initial magnesium sulphate course and the need for reinstitution of therapy was 29 h (4-168).

Evidence statement

Evidence from a prospective cohort study [EL 2+] showed early gestational age and higher arterial blood pressure to be predictors of the need for re-instituting magnesium sulphate postnatally in women with hypertensive disorders of pregnancy.
Investigation and management of women with pre-eclampsia in the postnatal period

There was no evidence 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 have 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 postpartum period.

The study examining the re-institution of magnesium sulphate is difficult to translate to any recommendation, and the GDG feels that such a decision should depend on clinical circumstances.

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.

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 further specialist investigations

Recommendations

Blood pressure

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

- at least four times a day while the woman is an inpatient
- 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 recently given birth, aim to keep blood pressure below 140/90 mmHg.

In women with pre-eclampsia who did not receive antihypertensive treatment and have recently given birth, start antihypertensive treatment for the first time if blood pressure is higher than 150/100 mmHg.
Ask women with pre-eclampsia who did not receive antihypertensive treatment and have recently given birth about severe headache and epigastric pain each time blood pressure is measured.

In women with pre-eclampsia who received antihypertensive treatment and have just 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 discharge from hospital until the woman is off treatment and has no hypertension.

In women with pre-eclampsia who have received antihypertensive treatment and have recently given birth, consider reducing antihypertensive treatment when their blood pressure falls below 140/90 mmHg.

In women with pre-eclampsia who have received antihypertensive treatment and have recently given birth, reduce antihypertensive treatment when blood pressure falls below 130/80 mmHg.

In women with pre-eclampsia who have received antihypertensive treatment and have just given birth, continue use of antenatal antihypertensive treatment.

If a woman has received methyldopa to treat pre-eclampsia, stop within 2 days of birth.

For women with pre-eclampsia who have recently given birth and are being discharged from hospital, write a care plan that includes all of the following:

- frequency of blood pressure monitoring
- thresholds for reducing or stopping treatment
- indications for early referral to primary care for blood pressure review.

In women who have pre-eclampsia and remain on antihypertensive treatment 2 weeks after discharge from hospital, perform medical review.

In women who have had pre-eclampsia perform medical review at the postnatal visit (6–8 weeks after the birth).

Refer women who have had pre-eclampsia and who still require antihypertensive treatment at the postnatal visit (6–8 weeks after the birth) for specialist assessment.

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 if results are normal at 48-72 hours.

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

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35 Methyldopa is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPC (August 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.
In women with pre-eclampsia, repeat platelet count, transaminases and serum creatinine measurements as clinically indicated if biochemical and haematological indices are not improving relative to pregnancy ranges.

In women with pre-eclampsia, carry out a urine dipstick test at the postnatal visit (6–8 weeks after the birth).

In women with pre-eclampsia who have recently given birth, do not measure fluid balance when creatinine is within the normal range.

In women who still require antihypertensive treatment at the postnatal visit (6–8 weeks after the birth) carry out further evaluation of renal function if urine protein is 2+ or more.
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 \(^{156,157}\) , both 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 Africa \(^{157}\) [EL 1+] assessed whether the results of Doppler umbilical artery velocimetry were beneficial to the management of a high risk pregnancy. Recruited patients 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=69) 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, 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 (4/47 versus 1/42: RR=3.57, 95% CI 0.42 to 30.73), antenatal fetal distress (2/47 versus 1/42: RR=1.79, 95% CI 0.17 to 19.01) or NICU admissions (12/47 versus 11/42: 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 the Canada 156 [EL 1+] compared the use of umbilical artery Doppler with non-stress test in women with high risk pregnancy (N=1,340). Participants were ≥ 32 weeks who had hypertensive disorders, diabetes that required insulin, suspected IUGR, postdates or patient-perceived decrease in fetal movement for > 24 hours. Excluded 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 review 158 [EL 1++] and an additional later RCT156 [EL 1+].

The systematic review 158 [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, on used PI and 3RCTs used systolic/diastolic ratio.

Perinatal mortality of non-malformed singletons was significantly less in babies born for high-risk women monitored with umbilical Doppler (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 Canada [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, 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. There is a lack of evidence about the timing of the test and the frequency with which it should be repeated.
8.4 Cardiotocography

Clinical effectiveness

One Cochrane systematic review [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 oestriol 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.

8.5 Routine versus computerised cardiotocography in severe pre-eclampsia

Clinical effectiveness

One RCT [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. Patients of GA 28-31 weeks were randomised separately from the group of 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 review [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 for 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 (1RCT, 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 review \textsuperscript{160} [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 Apgar5 score < 7 at or after 5-min, 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 review \textsuperscript{161} [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 inductions 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.

8.8 **Fetal movements**

**Clinical effectiveness**

One multicentre RCT [EL 1+] 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). No further description of the sample studied was 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 (M.D 2.0 per 100 women, 95% CI 1.8 to 5).

**Evidence statement**

One RCT 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 routinely counting group, however,
were more prone to feeling anxious in late pregnancy.
GDG interpretation of the evidence

Formal fetal movement counting conferred no benefit in terms of reduced perinatal mortality or interventions. However women should be encouraged to be aware of their baby’s movements.

8.9 Uterine artery Doppler velocimetry in high-risk pregnancies

Clinical effectiveness

Seven diagnostic studies [EL II] 63-67,163,164 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 different 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), A/C ratio (albumin/C=creatinine ratio).

We presented our results by population stratified according to risk factors: 1) previous pre-eclampsia, 2) chronic hypertension (see Section 3.5.1), 3) renal disease and 4) mixed risks.

8.9.1 Women with previous pre-eclampsia

One prospective diagnostic study 163 [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 patients 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 renal disease

One prospective diagnostic study 164 [EL II] used uterine Doppler (19-24 weeks gestation) in pregnant women with known renal disease (other than diabetic nephropathy; see Table 8.1). Renal function was considered decreased if two out of following three are abnormal - plasma creatinine (≥0.09 mmol/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 patients 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 renal disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Demographic characteristics</th>
<th>GA</th>
<th>Index</th>
<th>PE</th>
<th>IUGR</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous PET</td>
<td></td>
<td></td>
<td>RI: Abnormal = &gt;0.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frusca 1996</td>
<td>N=56 previous PET</td>
<td>24  wks</td>
<td>Sens: Spec: PPV: NPV:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country: Italy</td>
<td></td>
<td></td>
<td>100%</td>
<td>60%</td>
<td>15%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td></td>
<td>RI: abnormal &gt; 90th percentile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrier 1994</td>
<td>N= 51 with renal disease (other than diabetic nephropathy)</td>
<td>19-24 wks</td>
<td>Sens: Spec: PPV: NPV:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Country: New Zealand</td>
<td></td>
<td></td>
<td>50%</td>
<td>75%</td>
<td>14%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Women with mixed high risk factors

Three diagnostic studies 65-67 (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, renal 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 studies 67 (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

<table>
<thead>
<tr>
<th>Study</th>
<th>Population Demographic characteristics</th>
<th>GA</th>
<th>Parameters</th>
<th>PE</th>
<th>IUGR</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parretti 2003 Country: Italy</td>
<td>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)</td>
<td>24 wks</td>
<td>RI: abnormal ≤ 0.58</td>
<td>Sens: 77.8%</td>
<td>67.6%</td>
<td>44.4%</td>
</tr>
<tr>
<td>Caforio 1999 Country: Italy</td>
<td>N=336, 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±4.8 yrs</td>
<td>N=249 at 22-24 wks</td>
<td>RI: abnormal &gt; 90th percentile</td>
<td>Sens: 97%</td>
<td>71%</td>
<td>31%</td>
</tr>
<tr>
<td>Coleman 2000 Country: New Zealand</td>
<td>N=116, CH (n=69), previous recurrent PE (n=24), previously early-onset PE requiring delivery at ≤ 32 weeks (n=25), previous placental abruption (n=10), renal disease (n=40), SLE (n=13), antiphospholipid syndrome (n=5) Age: 31 (19-43) yrs. 31/116 were nulliparous and 18% smoked during pregnancy.</td>
<td>22-24 wks</td>
<td>RI: any abnormal &gt;0.58</td>
<td>Sens: 91%</td>
<td>42%</td>
<td>37%</td>
</tr>
</tbody>
</table>

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 renal disease: 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 renal 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 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 allow clinicians to alter individual patient management in this group of women based on normal or abnormal uterine artery Doppler between 20 and 24 weeks. Given that this group of women are already advised to take aspirin, the GDG cannot find any clinical intervention that discrimination by Doppler would drive or that would alter outcomes.

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, do not carry out cardiotocography if fetal activity is normal.

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, do not carry out cardiotocography if fetal activity is normal.

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 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:

- a change in the woman’s perception of 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 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, inform 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 monitoring
- fetal indications for birth and whether and when antenatal steroids should be given
- discussion with neonatal paediatricians and obstetric anaesthetists.

Women at high risk of pre-eclampsia

In women who are at a high risk of pre-eclampsia, do not use uterine artery Doppler velocimetry.

Carry out ultrasound fetal growth and amniotic fluid volume assessment and umbilical artery Doppler velocimetry starting at between 28 and 30 weeks (or 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 requiring birth before 34 weeks.
• pre-eclampsia with a baby born <10th centile
• intrauterine death
• placental abruption.

In women who are at a high-risk of pre-eclampsia, do not carry out cardiotocography if fetal activity is normal.

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 predictor of pre-eclampsia, but 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, renal 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. Trial should be stratified for risk factor.
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. The frequency of blood pressure monitoring in severe hypertension in this setting is examined in Section 8. Severe hypertension can develop from mild to moderate hypertension can in the course of labour. Therefore the GDG feels that women with mild to moderate hypertension should have their blood pressure measured more frequently.

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.

Measure blood pressure hourly during labour in women with mild or moderate hypertension.
In women with hypertension in pregnancy, continue use of existing 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 RCTs. All RCTs compared epidural with intravenous analgesia. Populations, however, were different for each trial: hypertensive disorders during pregnancy [EL=1+] [165], pre-eclampsia [EL=1+] and severe pre-eclampsia [166] [EL=1+] (see table 9.1).

Women with hypertensive disorders in pregnancy

A RCT [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 ≥ 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 patient 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 i.v 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 ±50 versus 40 ±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 ±18 versus 13 ±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 i.v fluids (1525 ±859 versus 954 ±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 RCT 165 [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 RCT 166 [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. Incidents 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

<table>
<thead>
<tr>
<th>Study</th>
<th>EL</th>
<th>N</th>
<th>Population</th>
<th>Exclusion</th>
<th>Intervention: Epidural analgesia</th>
<th>Comparison:</th>
</tr>
</thead>
</table>
| Lucas et al 167 | 1+ | 738   | Pregnancy induced hypertension \(dBP \geq 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 165 | -1| 200   | 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 HCI 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 166  | 1+ | 116   | Severe pre-eclampsia (singleton; vertex; >24 wks; dilation <5 cm) | -Platelet count < 80x109/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/hr). [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**

Pregnancy-induced 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 (i.m 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.

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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.
Advise operative birth in the second stage of labour for women with severe hypertension who have 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 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 studies [EL=1++] were identified, 168-173 two of which were large double-blind RCTs 172;173. The remaining four studies were Cochrane systematic reviews.168-171

Women with pre-eclampsia

Magnesium sulphate versus none/placebo

A Cochrane systematic review 171 [EL=1++] investigated the differential effects of magnesium sulphate (intramuscular or intravenous) when compared with none/placebo for the care of women with pre-eclampsia. A subgroup analysis by severity of pre-eclampsia was also conducted. Severe pre-eclampsia was defined by either having ≥ 2 signs...
or symptoms of imminent eclampsia, or proteinuria or, if on antihypertensive agents, 150/110 mmHg and 2+ proteinuria, or if the authors described them as having severe pre-eclampsia. Those who did not meet any of those criteria were classified as not having severe pre-eclampsia.

Six RCTs were included in the review (n=11,444 women). One multi-centre trial (Magpie Trial 2002) comprised 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 (3RCTs, 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 renal dialysis. Stillbirths and neonatal deaths rate was not different between the two groups.

Women with mild/moderate pre-eclampsia

Results for the mild/moderate pre-eclampsia subgroup showed that magnesium sulphate was better than none/placebo in preventing eclampsia (4RCTs, 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) 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. In the Magpie trial, 7927 women with pre-eclampsia before birth or 24 hours postpartum (DBP ≥ 90 mmHg, SBP ≥ 140 mmHg, ≥ 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 publication from the same 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 for 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 4 were ordered. Only one study met the inclusion criteria 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. Results were reported in U.S. dollars 2001, we converted the costs to £ 2009 using CPI conversion calculator. 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 health care expenditure per pregnancy was outweighed by 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).

Women with eclampsia

Three Cochrane systematic reviews studied the use of magnesium sulphate in women with eclampsia compared with diazepam, phenytoin and lytic cocktail. For a better overview of the available evidence, results for the primary outcomes of these reviews are presented in table 10.1a (maternal outcomes) and table 10.1b (fetal outcomes).

**Magnesium sulphate versus diazepam**

A Cochrane systematic review [EL= 1++] investigated the effects of magnesium sulphate (intramuscular or intravenous) when compared with diazepam. Participants were women with eclampsia at trial entry.
irrespective of whether they were before or after delivery, had singleton or multiple pregnancies, or whether an anticonvulsant had been given 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 regiments all included a loading dose and maintenance therapy. Three trials are of good quality. For four it is unclear whether concealment of allocation was adequate. One study is only available as an unpublished report, another as an abstract and an unpublished report. Blinding of the allocation after randomisation was not possible in any of the trials due to the nature of the drugs.

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) >7 days (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 for 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).

A Cochrane systematic review[169] 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 comprises women with antepartum eclampsia - only 17% were postpartum. About 80% of the women had had an anticonvulsant before trial entry. Five trials were small, and one was large (Collaborative Trial 1995). This large study included 777 of the 897 women in this review (87%). The methodological quality of the large trial was good, but for the small trials concealment of allocation was either inadequate or unclear. Blinding after randomisation was not possible in any of the trials, due to the nature of the drugs.

The recurrence of convulsions was significantly less in the magnesium sulphate group compared to the phenytoin group (5RCTs, 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 (1RCT, N=775: RR=0.67, 95% CI 0.50 to 0.89). They were also less likely to be given supportive mechanical ventilation (1RCT, N=775: RR=0.66, 95% CI 0.49 to 0.90), (Table 10.1)

Babies born to women treated with magnesium sulphonate were significantly less likely to be admitted to special care baby units, to stay there for more than 7 days or to die there after >7 days [(1RCT, N=518: RR=0.73, 95% CI 0.58 to 0.91), (1RCT, N=518: RR=0.53, 95% CI 0.33 to 0.86) and (1RCT, N=643: RR=0.77, 95% CI 0.63 to 0.95), respectively]. Furthermore, fewer babies born to magnesium sulphonate 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 review\textsuperscript{170} [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)

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>Evidence</th>
<th>Maternal death</th>
<th>Recurrence of convulsions</th>
<th>Admission to ICU</th>
<th>Coma &gt; 24 hrs</th>
<th>Respiratory depression</th>
<th>Pulmonary oedema</th>
<th>Pneumonia</th>
<th>Mechanical ventilation</th>
<th>Renal failure</th>
<th>Stroke</th>
<th>HELLP syndrome</th>
<th>Placental abruption</th>
<th>Cardiac arrest</th>
</tr>
</thead>
<tbody>
<tr>
<td>MgSO4 versus diazepam</td>
<td>Cochrane review 168</td>
<td>8RCTs, N=1336: RR=0.59 (0.37 - 0.94)</td>
<td>7RCTs, N=1411: RR=0.44 (0.34 - 0.57)</td>
<td>2RCTs, N=974: RR=0.80 (0.60 - 1.08)</td>
<td>–</td>
<td>3 RCTs, N=1025: RR=0.86 (0.57 - 1.30)</td>
<td>2 RCTs, N=974: RR=0.99 (0.39 - 2.55)</td>
<td>4 RCTs, N=1125: RR=0.64 (0.31 - 1.33)</td>
<td>3 RCTs, N=1025: RR=0.73 (0.45 - 1.18)</td>
<td>4 RCTs, N=1125: RR=0.87 (0.54 - 1.39)</td>
<td>3 RCTs, N=1025: RR=0.64, (0.33 - 1.23)</td>
<td>–</td>
<td>–</td>
<td>3 RCTs, N=1025: RR=0.94 (0.47 - 1.88)</td>
</tr>
<tr>
<td>MgSO4 versus phenytoin</td>
<td>Cochrane review 169</td>
<td>2 RCTs, N=797: RR=0.50 (0.24 - 1.05)</td>
<td>5 RCTs, N=895: RR=0.31 (0.20 - 0.47)</td>
<td>1 RCTs, N=775: RR=0.67 (0.50 - 0.89)</td>
<td>–</td>
<td>1 RCTs, N=775: RR=0.76 (0.46 - 1.09)</td>
<td>2 RCTs, N=825: RR=1.00 (0.47 - 2.10)</td>
<td>1 RCT, N=775: RR=0.44 (0.24 - 0.79)</td>
<td>1 RCT, N=775: RR=0.66 (0.49 - 0.90)</td>
<td>2 RCTs, N=825: RR=1.48 (0.94 - 2.32)</td>
<td>1 RCTs, N=775: RR=0.54 (0.20 - 1.46)</td>
<td>–</td>
<td>–</td>
<td>1RCT, N=775: RR=1.16 (0.39 - 3.43)</td>
</tr>
<tr>
<td>MgSO4 versus lytic cocktail</td>
<td>Cochrane review 170</td>
<td>2RCTs, N=199</td>
<td>–</td>
<td>2 RCTs, N=1108: RR=0.04 (0.00 - 0.74)</td>
<td>–</td>
<td>1 RCT, N=1108: RR=0.10 (0.01 - 0.76)</td>
<td>1 RCT, N=1108: RR=0.22 (0.01 - 4.54)</td>
<td>1 RCT, N=1108: RR=0.35 (0.14 - 80.36)</td>
<td>1 RCT, N=1108: RR=0.84 (0.20 - 3.57)</td>
<td>1RCT, N=1108: RR=0.22 (0.01 - 4.54)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

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

### Table 10.1b Magnesium sulphate for eclampsia (fetal outcomes)

<table>
<thead>
<tr>
<th>Fetal outcomes</th>
<th>Evidence</th>
<th>Death of fetus or infant</th>
<th>Utilisation of SCBU</th>
<th>Death in SCBU &gt; 7 days</th>
<th>Intubation at place of birth</th>
<th>Apgar score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stillbirth</td>
<td>Perinatal death</td>
<td>Neonatal death</td>
<td>Admission</td>
<td>Stay &gt; 7 days</td>
</tr>
<tr>
<td>MgSO4 versus diazepam</td>
<td>Cochrane review 168</td>
<td>4 RCTs, N=756: RR=0.89 (0.63 - 1.26)</td>
<td>3 RCTs, N=745: RR=1.04 (0.88 - 1.38)</td>
<td>3 RCTs, N=716: RR=1.34 (0.90 - 2.00)</td>
<td>3 RCTs, N=631: RR=0.99 (0.61 - 1.59)</td>
<td>3 RCTs, N=631: RR=0.56, (0.46 - 0.95)</td>
</tr>
<tr>
<td>MgSO4 versus phenytoin</td>
<td>Cochrane review 169</td>
<td>2RCTs, N=665: RR=0.85 (0.61 - 1.13)</td>
<td>2RCTs, N=665: RR=0.85 (0.59 - 1.53)</td>
<td>2 RCTs, N=665: RR=0.95 (0.69 - 1.30)</td>
<td>1 RCT, N=518: RR=0.73 (0.58 - 0.91)</td>
<td>1 RCT, N=518: RR=0.53 (0.33 - 0.86)</td>
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<tr>
<td>MgSO4 versus lytic cocktail</td>
<td>Cochrane review 170</td>
<td>2RCTs, N=117: RR=0.55 (0.26 - 1.16)</td>
<td>Fetal or infant death</td>
<td>2 RCTs, N=117: RR=0.45 (0.26 - 0.79)</td>
<td>2 RCTs N=1183: RR=0.39 (0.14 - 1.06)</td>
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</tbody>
</table>

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 > 7 days, 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 7 days or to die there after >7 days.

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**

There was clear evidence from RCTs and systematic reviews that Mg SO4 treatment in eclampsia reduced the incidence of further eclamptic fits. The evidence supported the use of magnesium sulphate in severe pre-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. There was clear evidence from systematic reviews that phenytoin, diazepam and lytic cocktails were not as effective as magnesium sulphate in preventing further eclamptic fits.

**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.

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

- hypertension and proteinuria and
- symptoms of severe headache or
- liver tenderness or
- visual disturbance or
- platelet count falling to below 100 x 10^9 per litre or
- epigastric pain or vomiting or
- abnormal liver enzymes (ALT or AST rising to above 70 iu/litre) or
- signs of clonus or
Use the Collaborative trial regimen for administration of magnesium sulphate:* 

- loading dose of 4 g should be given by infusion pump over 5–10 minutes, followed by a further infusion of 1 g/hour maintained for 24 hours after the last seizure
- recurrent seizures should be treated with either a further bolus of 2 g magnesium sulphate* or an increase in the infusion rate to 1.5 g or 2.0 g/hour.

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. 177-184

One of these studies was a Cochrane systematic review [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, nicardipine 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+] 179,182-184 and two [EL=1-] 180,181. 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 178 [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 patients 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 10.3 illustrates an overview of the available
evidence; results for the primary outcomes of all included studies are
presented in a series of tables (Table 10. 4 - 10).

Tables 10.4- 9 looked at the comparisons when evidence was available
from ≥2 difference sources (Cochrane review, the meta-analysis or extra
individual trials).

Tables 10.10 and11 looked at comparisons when evidence is available
from one source.

Labetalol versus hydralazine

Cochrane review (3 RCTs, N=69) [EL=1++] 177:

No significant differences were found between the two drugs.

Meta-analysis (5 RCTs, N=156) [EL=1++] 178:

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+] 179:

This is a non-blinded randomised trial from Panama. The study included
200 women with severe hypertension (BP≥ 160/110 mmHg), of ≥ 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++] 177:

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++] 178:

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-] 180:**

This is a non-blinded quasi-randomised trial (patients numbered as they attended: even numbers/hydralazine, odd numbers/nifedipine) from Ghana. The study included 79 women with severe pre-eclampsia (BP ≥ 160/110 mmHg, proteinuria ≥ 1+), who were ≥ 28 weeks. Nifedipine was given sublingually (10 mg capsule). This was repeated every 30 min if BP was ≥ 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-] 181:**

This is a small non-blinded quasi-randomised trial from Jamaica. The study included 39 women with severe pre-eclampsia (BP ≥ 160/110 mmHg, proteinuria ≥ 1+), who were ≥ 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++] 177:

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++] 178:
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++] 177:
No significant differences were found.
Meta-analysis (2RCTs, N=59) [EL=1++] 178:
No significant differences were found.

Prostacyclin versus hydralazine

Cochrane review (1RCT, N=47) [EL=1++] 177:
No significant differences were found.
Meta-analysis (1RCTs, N=59) [EL=1++] 178:
No significant differences were found.

Labetalol versus calcium channel blockers

Cochrane review (1RCT, nicardopine N=60) [EL=1++] 177
No significant differences were found.

Individual RCT: 182 [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 methylldopa

Cochrane review (1RCT, N=74) [EL=1++] 177:
No significant differences were found.

Labetalol versus diazoxide

Cochrane review (1RCT, N=90) [EL=1++] 177:
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++] 177:
No significant differences were found.

Nifedipine versus chlorpromazine

Cochrane review (1RCT, N=60) [EL=1++] 177:
No significant differences were found.
Cochrane review (1RCT, N=130) [EL=1++] 177:
Nifedipine versus prazonsin
No significant differences were found.

Cochrane review (2RCT, N=1683) [EL=1++] 177:
Nimodipine versus magnesium sulphate
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: 183[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: 184 [EL=1+] (n=32, 16 each arm)
This was a double blind RCT from Mexico. Women ≥ 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 (5µg/minute) with increases in dose of 5µg/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

<table>
<thead>
<tr>
<th></th>
<th>Hydralazine</th>
<th>Labetalol</th>
<th>Ca blockers</th>
<th>Ketanserin</th>
<th>Urapidil</th>
<th>Prostacyclin</th>
<th>Diazoxide</th>
<th>Methyldopa</th>
<th>Nitrates</th>
<th>Chlorpromazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>N/A</td>
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<td></td>
<td>M [EL 1+]</td>
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<td>M [EL 1++]</td>
<td>M [EL 1+]</td>
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<tr>
<td>Labetalol</td>
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<td>C [EL 1++]</td>
<td>M [EL 1++]</td>
<td>N/A</td>
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<td>C [EL 1++]</td>
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<td></td>
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<td>M [EL 1++]</td>
<td>M [EL 1+]</td>
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<td>C [EL 1++]</td>
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<tr>
<td>Ca blockers</td>
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<td>M [EL 1++]</td>
<td>M [EL 1+]</td>
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<td></td>
<td></td>
<td></td>
<td>C [EL 1++]</td>
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<tr>
<td></td>
<td>C [EL 1++]</td>
<td>M [EL 1+]</td>
<td>M [EL 1+]</td>
<td>N/A</td>
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<td>C [EL 1++]</td>
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<td>2x[EL 1+]</td>
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</table>
Table 10.3. Labetalol versus hydralazine, evidence: Cochrane review, meta-analysis and individual trials

<table>
<thead>
<tr>
<th>Labetalol versus hydralazine</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypotension</th>
<th>Side effects for the women</th>
<th>Caesarean section</th>
<th>Placental abruption</th>
<th>Pulmonary Edema</th>
<th>Other maternal outcomes</th>
<th>Fetal heart rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrome</th>
<th>Apgar &lt; 7</th>
<th>Admission to NICU</th>
<th>Admission to NICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane 177/98 [EL 1++]</td>
<td>3RCTs, N=69</td>
<td>1RCT, N=20 no cases</td>
<td>1RCT, N=20: RR=3.00 (0.79-11.44)</td>
<td>2RCTs, N=50 no cases</td>
<td>2RCTs, N=50: RR=0.52 (0.24-1.11)</td>
<td>3RCTs, N=69: RR=0.71 (0.40-1.24)</td>
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<tr>
<td>Magee et al 178/09 [EL 1++]</td>
<td>5RCTs, N=156</td>
<td>-</td>
<td>4RCTs, N=126: RR=3.41 (1.0-12.5)</td>
<td>4RCTs, N=122: RR=0.2 (0.0, 0.9)</td>
<td>5RCTs, N=156: RR=0.3 (0.2, 0.6)</td>
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<tr>
<td>Vigil-De et al 179/10 [EL 1+]</td>
<td>Individual RCT, N=200</td>
<td>100 versus 100 no cases</td>
<td>5/100 versus 51/100: RR=1.00 (0.30, 3.35)</td>
<td>0/100 versus 2/100, NS</td>
<td>18/100 versus 10/100, RR=1.80 (0.87, 3.70)</td>
<td>1/100 VS. 0/100, NS</td>
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</tbody>
</table>

Admission to NICU: Neonatal hypoglycaemia: 2RCTs, N=39: RR=1.14 (0.19-6.94)
### Table 10.4 Calcium channel blockers versus hydralazine, evidence: Cochrane review, meta-analysis and individual trials

<table>
<thead>
<tr>
<th>Ca blockers versus hydralazine</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypotension</th>
<th>Side effects for the women</th>
<th>Cesarean section</th>
<th>Placental abruption</th>
<th>Pulmonary oedema</th>
<th>Other maternal outcomes</th>
<th>Fetal heart rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrome</th>
<th>Apgar &lt; 7</th>
<th>Admission to NICU</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane 177/EL 1+* [177]</td>
<td>6 RCTs, N= 313</td>
<td></td>
<td>5 RCTs, N=263: RR=0.33 (0.15 - 0.70)</td>
<td>3 RCTs, N=198: RR=2.83 (0.12 - 0.84)</td>
<td>4 RCTs, N=236: RR=0.79 (0.50 - 1.24)*</td>
<td>1 RCT, N=37: RR=0.85 (0.56 - 1.29)</td>
<td>3 RCTs, N=203: RR=0.40 (0.09 - 1.83)</td>
<td>4 RCTs, N=161: RR=1.36 (0.42 - 4.41)</td>
<td>4 RCTs, N=161: RR=1.36 (0.42 - 4.41)</td>
<td>–</td>
<td>–</td>
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<td></td>
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</tr>
<tr>
<td>Magee et al 178/EL 1+</td>
<td>9 RCTs, N=619</td>
<td></td>
<td>5 RCTs, N=350: RR=0.7 (0.5, 1.1)</td>
<td>6 RCTs, N=485: RR=0.4 (0.1, 2.0)</td>
<td>4 RCTs, N=245: RR=1.1 (0.8, 1.5)</td>
<td>–</td>
<td>6 RCTs, N=360: RR=0.2 (0.1, 0.6)</td>
<td>Stillbirth: 6 RCTs, N=388: RD= -0.01 (0.03 to +0.02)</td>
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<tr>
<td>Kwawukume et al 180/EL 1-</td>
<td>Individual RCT, N=79</td>
<td></td>
<td>5/44 versus 14/35, RR=0.28 (0.11 - 0.71)</td>
<td>–</td>
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<td>22/44 versus 24/35, RR=0.73 (0.50, 1.06)</td>
<td>–</td>
<td>0/44 versus 2/35, NS</td>
<td>0/44 versus 1/35, NS</td>
<td>–</td>
<td>11/44 versus 13/35, RR=0.67 (0.34, 1.31)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fletcher et al 181/EL 1-</td>
<td>Individual RCT, N=39</td>
<td></td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>3/20 versus 2/19, RR=1.43 (0.27, 7.61)</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td></td>
</tr>
</tbody>
</table>

*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=240: RR=1.08, 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
<table>
<thead>
<tr>
<th>Ketanserin versus hydralazine</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypertension</th>
<th>Side effect for the women</th>
<th>Caesarean section</th>
<th>Placental abruption</th>
<th>Pulmonary oedema</th>
<th>Other maternal outcomes</th>
<th>Fetal heart rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrome</th>
<th>Apgar &lt; 7</th>
<th>Admission to NICU</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cochrane [EL 1++]</strong></td>
<td>4 RCTs, N=200</td>
<td>2 RCTs, N=64:</td>
<td>2 RCTs, N=120:</td>
<td>3 RCTs, N=180:</td>
<td>2 RCTs, N=76:</td>
<td>3 RCTs, N=120:</td>
<td>2 RCTs, N=64:</td>
<td>1 RCT, N=44:</td>
<td>Maternal death: 2 RCTs, N=124:</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>RR=0.60 (0.08-4.24)</td>
<td>RR=0.3 (0.14-0.53)</td>
<td>RR=0.26 (0.07-1.03)</td>
<td>RR=0.53 (0.14-2.06)</td>
<td>RR=0.14, 95% CI 0.02 to 1.10</td>
<td>RR=0.11 (0.01-1.95)</td>
<td>RR=0.32, 95% CI 0.03 to 2.96</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Magee et al [EL 1++]</td>
<td>4 RCTs, N=190</td>
<td>-</td>
<td>2 RCTs, N=47:</td>
<td>2 RCTs, N=64:</td>
<td>2 RCTs, N=64:</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2 RCTS, N=180:</td>
<td>RR=0.27 (0.05-1.64)</td>
<td>-</td>
<td>-</td>
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<tr>
<td></td>
<td></td>
<td>RR=1.3 (0.7, 2.6)</td>
<td>RR=0.4 (0.1, 1.4)</td>
<td>RR=0.4 (0.2, 0.7)</td>
<td>RR=0.4 (0.1, 1.4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>RR=0.4 (0.1, 1.4)</td>
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</tr>
</tbody>
</table>
### Table 10.6 Urapidil versus hydralazine, evidence: Cochrane review and meta-analysis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypotension</th>
<th>Side effects for the women</th>
<th>Caesarean section</th>
<th>Placental abruption</th>
<th>Pulmonary Oedema</th>
<th>Other maternal outcomes</th>
<th>Fetal heart rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrome</th>
<th>Apgar &lt; 7</th>
<th>Admission to NICU</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urapidil</td>
<td>2 RCTs, N=59</td>
<td>1 RCT, N=26 no cases</td>
<td>2, N=59: RR=1.38 (0.06-31.14)</td>
<td>1, N=33: RR=0.22 (0.02-2.13)</td>
<td>2, N=59: RR=0.59 (0.10-3.58)</td>
<td>2, N=59: RR=0.77 (0.51-1.16)</td>
<td>1 RCT, N=33: RR=0.15 (0.01-3.46)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>Stillbirth: 1 RCT, N=26 no cases</td>
<td>--</td>
<td>--</td>
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</tr>
<tr>
<td>Hydralazine</td>
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<td></td>
</tr>
<tr>
<td>Magee et al 178[EL 1+++]</td>
<td>2 RCTs, N=59</td>
<td>--</td>
<td>2, N=26 no cases</td>
<td>1, N=33: RR=0.2 (0.0, 2.1)</td>
<td>1 RCT, N=29: RR=1.4 (0.2, 11.1)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>2, N=55: RR=0.1 (0.0, 1.8)</td>
<td>Stillbirth: 2 RCT, N=56 no cases</td>
<td>--</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypotension</th>
<th>Side effects for the women</th>
<th>Caesarean section</th>
<th>Placental abruption</th>
<th>Pulmonary Oedema</th>
<th>Other maternal outcomes</th>
<th>Fetal heart rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrome</th>
<th>Apgar &lt; 7</th>
<th>Admission to NICU</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostacyclin</td>
<td>1 RCT, N=47</td>
<td></td>
<td>1 RCT, N=47: RR=0.23 (0.01 -4.47)</td>
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<tr>
<td>Hydralazine</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Magee et al 178[EL 1+++]</td>
<td>1 RCT, N=47</td>
<td></td>
<td>1 RCT, N=50: RR=0.2 (0.0, 4.5)</td>
<td>--</td>
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<td>--</td>
<td>--</td>
<td></td>
<td>1 RCT, N=47: RR=0.9 (0.5, 1.5)</td>
<td>Stillbirth: 1 RCT, N=47 no cases</td>
<td>--</td>
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</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Labetalol Vs. calcium channel blockers</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypotension</th>
<th>Side effects for the women</th>
<th>Caesarea n section</th>
<th>Placental abruption</th>
<th>Pulmonar y Oedema</th>
<th>Other maternal outcomes</th>
<th>Fetal hear rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrom e</th>
<th>Apgar &lt; 7</th>
<th>Admiss ion to NICU</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane 17/98 (Nicardopine)</td>
<td>1RCT, N=60</td>
<td>1,N=60: RR=1.22 (0.59-2.51)</td>
<td>–</td>
<td>1, N=60 no cases</td>
<td>* Specific side effects</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Vermilion et al 13 (Nifedipine)</td>
<td>Individual RCT, N=50 [EL 1+]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>** Specific side effects</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>

* 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: 2/25 versus 4/25, NS
- Flushing: 2/25 versus 2/25, NS
- Nausea: 2/25 versus 2/25, NS
- Umbilical artery pH <7.0: 1/15 versus 1/14, RR=1.07 (0.07, 15.54)
Table 10.9 Different antihypertensives comparisons, evidence: Cochrane review

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypotension</th>
<th>Side effects for the women</th>
<th>Caesarean section</th>
<th>Placental abruption</th>
<th>Pulmonary Oedema</th>
<th>Other maternal outcomes</th>
<th>Fetal heart rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrome</th>
<th>Apgar &lt; 7</th>
<th>Admission to NICU</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labetalol versus methyldopa Cochrane 177</td>
<td>1 RCT, N=74</td>
<td>1, N=72: RR=1.19 (0.74-1.94)</td>
<td>–</td>
<td>1, N=72: RR=0.85 (0.56-1.30)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1, N=72: RR=4.49 (0.22-90.33)</td>
<td>–</td>
<td>–</td>
<td>1 RCT, N=72: RR=1.06 (0.66-1.71)</td>
<td>–</td>
<td>Small for gestation</td>
<td>–</td>
</tr>
<tr>
<td>Labetalol versus diazoxide Cochrane 177</td>
<td>1 RCT, N=90</td>
<td>1, N=90: RR=0.50 (0.130-1.88)</td>
<td>1, N=90: RR=0.06 (0.00-0.99)</td>
<td>–</td>
<td>1, N=90: RR=0.43 (0.18-1.02)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1, N=90: RR=0.14 (0.01-2.69)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Nitrates versus MgSO4 Cochrane 177</td>
<td>1 RCT, N=36</td>
<td>1, N=36: RR=0.14, (0.01-2.58)</td>
<td>–</td>
<td>1, n=36: RR=0.19 (0.07-0.53)</td>
<td>–</td>
<td>–</td>
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</tr>
<tr>
<td>Nifedipine versus chlorpromazine Cochrane 177</td>
<td>1 RCT, N=60</td>
<td>1, N=55: RR=2.52 (0.11-59.18)</td>
<td>1, N=60: RR=0.09 (0.01-1.57)</td>
<td>–</td>
<td>1, N=55: RR=0.80 (0.60-1.05)</td>
<td>1 RCT, N=1650: RR=0.76 (0.27-2.18)</td>
<td>–</td>
<td>Stroke: 1 RCT, N=1650 no cases.</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Baby intubated at delivery: N=1650: RR=0.78 (0.49-1.23)</td>
<td>–</td>
</tr>
<tr>
<td>Nifedipine versus prazosin Cochrane 177</td>
<td>1 RCT, N=130</td>
<td>1, N=145 no cases</td>
<td>–</td>
<td>–</td>
<td>1, N=145: RR=0.90 (0.72 to 1.13)</td>
<td>1 RCT, N=145: RR=0.96 (0.40-2.28)</td>
<td>1 RCT, N=145: RR=0.19 (0.02-1.60)</td>
<td>–</td>
<td>1 RCT, N=149: RR=0.46 (0.18-1.13)</td>
<td>–</td>
<td>–</td>
<td>1 RCT, N=130: RR=0.78 (0.49-1.23)</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Nimodipine versus MgSO4 Cochrane 177</td>
<td>2 RCTs, N=1683</td>
<td>2, N=1683: RR=2.24 (1.06-4.73)</td>
<td>1, N=1650: RR=0.84 (0.76-0.93)</td>
<td>1, N=1650: RR=0.72, (0.23-2.27)</td>
<td><strong>Specific side effects</strong></td>
<td>2, N=1683: RR=0.97 (0.89-1.06)</td>
<td>–</td>
<td>–</td>
<td>–</td>
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</tr>
</tbody>
</table>

**Specific side effects:**
- Headache: 1 RCT, N=1650: RR=1.06, 95% CI 0.71 to 1.58
- Flushing: 1 RCT, N=1650: RR=0.22, 95% CI 0.12 to 0.40
- Nausea and/or vomiting: 1 RCT, N=1650: RR=0.86, 95% CI 0.59 to 1.24
### Table 10.10 Different antihypertensives comparisons, evidence: individual RCTs

<table>
<thead>
<tr>
<th>Drug Comparison</th>
<th>Total number of RCTs &amp; participants</th>
<th>Eclampsia</th>
<th>Persistent high blood pressure</th>
<th>Maternal hypertension</th>
<th>Side effects for the women</th>
<th>Caesarean section</th>
<th>Placental abruption</th>
<th>Pulmonary oedema</th>
<th>Other maternal outcomes</th>
<th>Fetal heart rate deceleration</th>
<th>Fetal or neonatal death</th>
<th>Respiratory distress syndrome</th>
<th>Apgar &lt; 7</th>
<th>Admission to NICU</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazoxide versus hydralazine Hennessy et al [183]</td>
<td>Individual RCT, N= 97 [EL 1+]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>38/50 versus 33/47&lt;br&gt;RR=1.08 (0.85, 1.36)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Non-reassuring CTG required delivery: 13/52 versus 12/49, RR=1.02 (0.52, 2.02)</td>
<td>1/52 versus 3/49, RR=0.31 (0.03, 2.92)</td>
<td>14/52 versus 13/49, RR=1.01 (0.53, 1.94)</td>
<td>At 5-min: 14/52 versus 4/49, RR=0.94 (0.25, 3.56)</td>
<td>–</td>
<td>Neonatal hypoglycaemia: 6/52 versus 5/49, R=1.13 (0.37, 3.47)</td>
</tr>
<tr>
<td>Nitroglycerine versus nifedipine Manzur-Verastegui et al [184]</td>
<td>Individual RCT, N=32 [EL 1+]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>* Specific side effects</td>
<td>11/16 versus 12/16, RR=0.92 (0.59, 1.42)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Post-delivery bleeding &gt; 1.000 ml: 1/16 versus 0/16, RR=0.33 (0.04, 2.88)</td>
<td>16 versus 16, no cases</td>
<td>–</td>
<td>At 1-min: 2/16 versus 7/16, NS&lt;br&gt;At 5-min: 1/16 versus 0/16, NS</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*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

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 situation to inform the GDG but the consensus was that lowering the blood pressure in severe hypertension is necessary. There did not appear to be any evidence that one particular antihypertensive 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 regimes. 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 IV for labetalol, oral for nifedipine and IV 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 and oral treatment was likely to be cheaper due to the extra costs of intravenous treatment.
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\(^{37}\) (oral or intravenous)
- hydralazine (intravenous)
- nifedipine\(^{38}\) (oral).

In women with severe hypertension who are in critical care, monitor their response to treatment:
- to ensure that blood pressure falls
- to identify adverse effects for both the woman and the fetus
- to modify treatment according to response.

Consider using up to 500ml 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, 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.

\(^{37}\) Labetalol is licensed for the treatment of hypertension, including during pregnancy and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise 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.

\(^{38}\) Nifedipine is licensed for the treatment of hypertension and is already used widely in UK obstetric practice, but the SPCs (August 2009) advise that it is contraindicated in pregnancy before week 20 and during breastfeeding, or that it must not be administered during the entire pregnancy and that the child should be weaned if treatment should be necessary during the lactation period, or that it should not be used in women who are or who may become pregnant and that it is not recommended during lactation, or that it should not be used in nursing mothers and women who are or who may become pregnant. Informed consent on the use of nifedipine in these situations should be obtained and documented.
pregnancy in the critical care setting. Comparisons should be made between the different anythypertensives, with assessment against outcomes such as persistence of severe hypertension after completion of therapy or by the need for additional treatment, maternal side effects and the effect on the fetus and baby.

10.4 Corticosteroids for fetal lung maturation

Clinical effectiveness

A Cochrane systematic review [EL=1++] investigated the effect of antenatal corticosteroids for accelerating fetal lung maturation for 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 with no treatment given to women prior to 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 significantly reduced risk of neonatal death (2RCTs, N=278 neonates: RR=0.50, 95% CI 0.29 to 0.87), respiratory distress syndrome (5RCTs, N=382: RR=0.50, 95% CI 0.35 to 0.72) and cerebroventricular haemorrhage (2RCTs, N=278 neonates: RR=0.38, 95% CI 0.17 to 0.87). They were also significantly less likely to need mechanical ventilation (1RCT, N=200: RR=0.62, 95% CI 0.41 to 0.91) or to have systemic infection in the first 48 hours of life (1RCT, N=200: 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 seen for combined fetal and neonatal death, fetal death, birthweight, chorioamnionitis or puerperal sepsis.

Evidence statement

A Cochrane review [EL=1++] showed that the use of 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.

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 to 37 weeks but the GDG consider that there is likely to be benefit. The preferred steroid is betamethasone 12 mg intramuscularly 24 hours apart.
### 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 at 35-36 weeks.

### 10.5 Corticosteroids in the management of HELLP syndrome

#### Clinical effectiveness

Corticosteroids have been used in women (antepartum and postpartum) diagnosed with HELLP syndrome. One Cochrane systematic review studied two comparisons: dexamethasone plus standard treatment versus standard treatment alone and dexamethasone versus betamethasone. One additional RCT compared dexamethasone with placebo while another RCT compared the use of dexamethasone and betamethasone.

Dexamethasone plus standard treatment versus standard treatment alone

A Cochrane review investigated the effects of corticosteroids in women with HELLP syndrome (diagnosed clinically and by biochemical parameters) during pregnancy or shortly after delivery. 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 RCT compared the efficacy of dexamethasone with placebo for the treatment of women (pregnant or puerperal) who developed hypertension during pregnancy and met the criteria for HELLP syndrome classes 1 and 2. 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 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 patients 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 [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 hyperbilirubinemia and mean time to discharge in days.

An American RCT [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 Netherlands\(^{89}\) [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 patient 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 hydroxyethylstarch (HES) 6% x2 a day over 4h. Antihypertensives (i.e. ketanserine) were used to achieve DBP 85-95 mmHg. Additional medication (oral labetalol, methyl dopa and nifedipine and occasionally intravenous dihydralazine) was used when necessary. Restricted amounts of NaCl 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 (methyl dopa) to achieve DBP between 95-105 mmHg. Additional medication (oral labetalol, nifedipine and intravenous ketanserine and occasional intravenous dihydralazine) was used when necessary. Restricted amounts of NaCl 0.9% were infused with intravenous medication.

MgSO\(_4\) 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 year [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 study [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 renal 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<10mmHg and/or cardiac index <3.5 l/min/m2, patients received i.v. 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, patients received i.v. dihydralazine (1mg/h), followed by hourly increments of 1mg. Methyldopa used when the desired reduction was not obtained. After stabilisation patients 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. Patients 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 dates babies. There were no obvious maternal advantages.

Confidential Enquiry into Maternal Deaths in the UK 1994-6 indicated 6 deaths due to adult respiratory distress syndrome (ARDS) which appeared to be related to poor fluid management in women with severe disease and recommendations made then which advised that senior medical involvement and care when intravenous fluids were being considered was essential. It is considered that this advice resulted in the fact that in the 2002-5 report no deaths due solely to fluid mismanagement and ARDS occurred.

**Recommendations**

Do not use volume expansion for women with severe pre-eclampsia except when hydralazine 39 is the antenatal antihypertensive.

In women with severe pre-eclampsia, limit total fluids to 80 ml/hour.

### 10.7 Operative birth (caesarean section) versus induction of labour

**Clinical effectiveness**

Caesarean section without labour versus labour induction

One Nigerian RCT 92 [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

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Hydralazine is licensed for use in pregnancy.
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 study 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 study 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 3 patients who had an unusually longed hospital stay (>400 hrs) for unrelated medical conditions (SLE nephritis in 2 patients, 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 scores ≤ 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 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

Refer women with pre-eclampsia to the appropriate critical care setting using the following criteria: 40

<table>
<thead>
<tr>
<th>Level 3</th>
<th>Severe pre-eclampsia and needing ventilation</th>
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<tbody>
<tr>
<td>Level 2</td>
<td>Step down from level 3 of severe pre-eclampsia with any of the following complications:</td>
</tr>
<tr>
<td></td>
<td>- eclampsia</td>
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<td></td>
<td>- HELLP syndrome</td>
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<td>- haemorrhage</td>
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<td>- hyperkalaemia</td>
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<td></td>
<td>- severe oliguria</td>
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<td>- coagulation support</td>
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*40 Taken from Intensive Care Society, Standards and Guidelines 2002.*
<table>
<thead>
<tr>
<th>Level 1</th>
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<tbody>
<tr>
<td></td>
<td>- intravenous antihypertensive treatment</td>
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<td></td>
<td>- initial stabilisation of severe hypertension</td>
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<td>- evidence of cardiac failure</td>
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<td>- abnormal neurology</td>
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<td></td>
<td>- Mild or moderate pre-eclampsia</td>
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<td></td>
<td>- Ongoing conservative antenatal management of severe pre-term hypertension</td>
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<tr>
<td></td>
<td>- Step-down therapy after the birth</td>
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</tbody>
</table>
11 Advice at discharge from maternity care

11.1 Introduction

The development of new hypertension during pregnancy will have had an impact on the woman’s experience of the pregnancy itself. Particularly if severe, it will have raised concerns about the woman’s future health and the prospects for a further pregnancy. Women will wish to discuss the events surrounding the pregnancy and learn whether there are lifestyle changes or therapies that would avoid or reduce the risk of a further pregnancy 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.

11.2 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.)\textsuperscript{16} \([\text{EL}=1++]\) 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 3488160 women, with 198252 affected by pre-eclampsia (exposure group). 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.)\textsuperscript{195} \([\text{EL}=1++]\) 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 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 11.1.

Risk of future hypertension

Bellamy et al.\textsuperscript{16} included 13 studies (21,030 women); 1885 women out of the 3658 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, I²=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) (χ² =8.48, p =0.004).

 Risk of ischaemic heart disease

Bellamy et al. included eight studies (2 346 997 women); 5097 women out 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 substantial heterogeneity was observed (P=0.21, I²=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.’s 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 (P=0% for each category)

Risk of cerebrovascular events (stroke)

Bellamy et al. included four studies (1,671,578 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; I²=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. 195 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. 16 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 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; I²=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, 0.9 to 2.2).

Risk of peripheral arterial disease

In the review by McDonald et al. 195, 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: 3 studies, RR=1.87, 95% CI 0.94 to 3.73).

Risk of cardiovascular mortality

Pooled estimates from 5 cohort studies McDonald et al. 195 showed that women with a history of pre-eclampsia/eclampsia were at 2.99 higher risk of dying of cardiovascular disease (RR=2.99, 95% CI 1.73 to 3.04).

Women with gestational hypertension

Bellamy et al. 16 included two studies, totalling 2106 women, to investigate the association between a history of pregnancy induced hypertension and future hypertension; 254 women had a 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 (0.82 to 13.92; P for heterogeneity=0.0006, I²=91.4%). The increase in risk for future cardiovascular disease was 1.66 (0.62 to 4.41; P for heterogeneity=0.10, I²=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 11.1 Summary of evidence for risk of long term cardiovascular disease

<table>
<thead>
<tr>
<th></th>
<th>Studies in pool estimate</th>
<th>Population</th>
<th>RR (95% CI)</th>
<th>µ follow up</th>
<th>Other factors related</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>13 cohort</td>
<td>PE</td>
<td>3.70 (2.70 to 5.05)</td>
<td>14.1 yrs</td>
<td>Pre-eclampsia in any &gt; 1st pregnancy</td>
</tr>
<tr>
<td>IHD</td>
<td>8 cohorts</td>
<td>PE</td>
<td>2.16, 1.86 to 2.52</td>
<td>11.7 yrs</td>
<td>Pre-eclampsia before 37 &gt; after 37 wks</td>
</tr>
<tr>
<td></td>
<td>10 cohorts</td>
<td>PE/E</td>
<td>2.33, 1.95-2.78</td>
<td></td>
<td>Severe &gt; moderate &gt; mild pre-eclampsia</td>
</tr>
<tr>
<td></td>
<td>4 case-controls</td>
<td>PE/E</td>
<td>OR= 2.47, 1.22-5.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>4 cohorts</td>
<td>PE</td>
<td>1.81, 1.45-2.27</td>
<td>10.4 yrs</td>
<td>Risk of fatal stroke &gt; non-fatal stroke</td>
</tr>
<tr>
<td></td>
<td>6 cohorts</td>
<td>PE/E</td>
<td>2.03, 1.54 to 2.67</td>
<td></td>
<td>Pre-eclampsia before 37 &gt; after 37 wks</td>
</tr>
<tr>
<td></td>
<td>1 case-control</td>
<td>PE/E</td>
<td>OR=2.6, 1.5 to 4.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>3 cohorts</td>
<td>PE</td>
<td>1.79, 1.37-2.33</td>
<td>4.7 yrs</td>
<td>Severe &gt; mild pre-eclampsia</td>
</tr>
<tr>
<td>PAD</td>
<td>3 cohorts</td>
<td>PE/E</td>
<td>1.87, 0.94 to 3.73</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality of CVD</td>
<td>5 cohorts</td>
<td>PE/E</td>
<td>2.99, 1.73 to 3.04</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GDG interpretation of the evidence

The evidence on the long term risk to women who have had pre-eclampsia is good quality with less information 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. 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 the 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 later cardiovascular disease. Increased surveillance in this group may, therefore, lead to earlier intervention, usually with antihypertensives, with likely benefits for the woman. The GDG therefore feels that such women should have enhanced surveillance of their blood pressure.

Recommendations

Advise women who have had pre-eclampsia that they are at increased risk of developing high blood pressure and its complications in later life and that they should have their blood pressure measured annually.

Advise women who have had gestational hypertension that they should have their blood pressure measured at least every 5 years.

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.

### 11.3 Long-term risk of end-stage renal disease

**Clinical effectiveness**

A large retrospective cohort study conducted in Norway [EL=2++] 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 (±SD) duration of follow-up after the first, second and third pregnancies were 26.5±7.5, 22.8±0.8 and 18.7±8.2 years, respectively. The mean ages of the mother at the first, second and third deliveries were 23.5±4.3, 26.9±4.3 and 30.2±4.3 years, respectively.

ESRD developed in 477 of 570,433 women a mean (±SD) of 17±9 years after the first pregnancy (overall rate, 3.7 per 100,000 women per year). Among women who had been pregnant one or more times, preeclampsia 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 preeclampsia, 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 renal disease developed in 477 of 570,433 women a mean (±SD) of 17±9 years after the first pregnancy (overall rate, 3.7 per 100,000 women per year).

Evidence suggested that among women who had been pregnant one or more times, pre-eclampsia during the first pregnancy was associated with a relative risk of ESRD of 4.7 (95% confidence interval [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, pre-eclampsia 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 11.2 Summary of evidence for risk of end-stage renal disease**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total No. of women</th>
<th>No. with ESRD</th>
<th>No./100,000 Person-Yr (95% CI)**</th>
<th>Adjusted Relative Risk (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>After first pregnancy (all women)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pre-eclampsia</td>
<td>549,515</td>
<td>410</td>
<td>3.3 (2.9 - 3.6)</td>
<td>14.5 (11.2 - 18.1)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td></td>
<td></td>
<td></td>
<td>4.3 (3.3 - 5.6)</td>
</tr>
<tr>
<td>After second pregnancy (women with 2 pregnancies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pre-eclampsia</td>
<td>456,884</td>
<td>266</td>
<td>2.8 (2.5 - 3.1)</td>
<td>8.6 (5.6 - 12.3)</td>
</tr>
<tr>
<td>Pre-eclampsia in first pregnancy only</td>
<td>14,588</td>
<td>25</td>
<td>16.8 (10.3 - 25.0)</td>
<td>5.3 (3.3 - 8.5)</td>
</tr>
<tr>
<td>Pre-eclampsia in second pregnancy only</td>
<td>6,120</td>
<td>20</td>
<td>15.4 (6.1 - 29.0)</td>
<td>4.7 (2.1 - 10.7)</td>
</tr>
<tr>
<td>Pre-eclampsia in both pregnancies</td>
<td>2,411</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After three pregnancies (women with 2 pregnancies)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No pre-eclampsia</td>
<td>198,192</td>
<td>84</td>
<td>2.4 (1.9 - 2.9)</td>
<td>14.4 (9.4 - 20.5)</td>
</tr>
<tr>
<td>Pre-eclampsia in one pregnancy only</td>
<td>10,727</td>
<td>26</td>
<td>6.0 (2.1 - 11.7)</td>
<td>5.8 (3.7 - 9.1)</td>
</tr>
<tr>
<td>Pre-eclampsia in first pregnancy only</td>
<td>5,930</td>
<td>6</td>
<td>16.2 (5.1 - 33.4)</td>
<td>7.3 (3.0 - 18.1)*</td>
</tr>
<tr>
<td>Pre-eclampsia in second pregnancy only</td>
<td>1,875</td>
<td>5</td>
<td>33.1 (14.9 - 73.9)</td>
<td>14.3 (8.2 - 24.7)*</td>
</tr>
<tr>
<td>Pre-eclampsia in third pregnancy only</td>
<td>2,922</td>
<td>15</td>
<td>32.9 (14.9 - 57.9)</td>
<td>10.9 (5.0 - 23.8)</td>
</tr>
</tbody>
</table>

**GDG interpretation of the evidence**

The risk of end stage renal 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**

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

### 11.4 Thrombophilia and the risk of pre-eclampsia

#### Clinical effectiveness

A health technology assessment (HTA, 2006)\(^{139}\) [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 heterozygous were significantly associated with pre-eclampsia (OR=2.54, 95% CI 1.52 to 4.23) and (OR=2.73, 95% CI 1.65 to 4.51), respectively.
While Factor V Leiden (FVL) homozygous 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: RR=1.91, 95% CI 1.60 to 2.28).

**Evidence statement**

HTA [EL=1++] looking at thrombophilia and risk of pre-eclampsia showed that pregnant women with the following thrombophilias have higher odds of developing pre-eclampsia:

<table>
<thead>
<tr>
<th>Thrombophilia</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperhomocysteinaemia</td>
<td>OR=3.49 (1.21 to 10.11)</td>
</tr>
<tr>
<td>Prothrombin heterozygous</td>
<td>OR=2.73 (1.65 to 4.51)</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>OR=2.54 (1.52 to 4.23)</td>
</tr>
<tr>
<td>FVL Heterozygotes</td>
<td>OR=2.34 (1.56 to 3.51)</td>
</tr>
<tr>
<td>MTHFR homozygous</td>
<td>OR=1.32 (1.05 to 1.66)</td>
</tr>
</tbody>
</table>

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 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: RR=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.
11.5 Risk of recurrence of hypertensive disorders of pregnancy

Clinical effectiveness

11.5.1 Previous pregnancy with gestational hypertension

Five retrospective cohort studies\textsuperscript{198-202} \([\text{EL}=2+]\) 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 \((n=2)\). The overall number of women included was 2,575. In two studies \textsuperscript{198,200}, index pregnancy was the first pregnancy and recurrence was investigated in the second pregnancy. In the other three studies \textsuperscript{199,201,202}, 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\% - 47\%. Pooled results from the five studies showed an overall 32\% \((814/2,575)\) risk of recurrence of gestational hypertension. As for recurrence of pre-eclampsia in subsequent pregnancy, it ranged between 2\% - 7\%. The incidence of gestational hypertension after a normotensive index pregnancy was 9.3\%. Pooled results from the five studies showed an overall risk of 3\% \((85/2,575)\) of having pre-eclampsia in subsequent pregnancy (Table 11.3).

Table 11.3 Summary of studies that presents the risk of recurrence of pregnancy related hypertension in women with gestational hypertension.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Participants</th>
<th>GH %(n)</th>
<th>PE %(n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjartardottir 2006</td>
<td>Iceland</td>
<td>n=511</td>
<td>47%(240)</td>
</tr>
<tr>
<td>Brown 2007</td>
<td>Australia</td>
<td>n=367</td>
<td>26%(95)</td>
</tr>
<tr>
<td>Hargood 1991</td>
<td>Australia</td>
<td>n=121</td>
<td>44%(53)</td>
</tr>
<tr>
<td>Campbell 1985</td>
<td>Scotland</td>
<td>n=1339</td>
<td>29%(388)</td>
</tr>
<tr>
<td>Zhang 2001</td>
<td>USA</td>
<td>n=237</td>
<td>16%(38)</td>
</tr>
<tr>
<td><strong>Total:</strong></td>
<td></td>
<td><strong>N=2,575</strong></td>
<td><strong>32%(814/2575)</strong></td>
</tr>
</tbody>
</table>

Previous pregnancy with pre-eclampsia

Nine retrospective cohort studies \textsuperscript{198-205} \([\text{EL}=2+]\) investigated the recurrence of hypertensive disorders of pregnancy in women with pre-eclampsia in index pregnancy. The studies were conducted in Iceland, Scotland, the USA \((n=2)\), Australia \((n=2)\), Norway, Denmark and Sweden. The overall number of women included was 55,105. In six studies \textsuperscript{198,200,203-205} \([\text{REF}]\), the index pregnancy was the first pregnancy and recurrence was investigated in the next \((2nd)\) pregnancy. In the other three studies \textsuperscript{199,201,202}, index pregnancy was not always first pregnancy and subsequent pregnancies were not always consecutive but only one subsequent pregnancy was included.

Risk of gestational hypertension in subsequent pregnancy ranged between 13\% - 53\%. Pooled results from the five studies which looked at this outcome showed an overall 25.9\% \((187/722)\) risk of recurrence of gestational hypertension. As for the risk of pre-eclampsia in subsequent pregnancy, it ranged between 0\% - 16\%. The incidence of pre-eclampsia after a normotensive index pregnancy was 0.7\%. Pooled results from the nine studies that looked at this outcome showed an overall risk of 14.5\% \((7975/55105)\) of having pre-eclampsia in subsequent pregnancy (table.2).

One large Swedish retrospective cohort study\textsuperscript{9} \([\text{EL}=2+]\) investigated risk of pre-eclampsia in pregnant women. Out of 763,795 women studied, 31417 had pre-eclampsia giving an incidence risk of 3.0\%. The risk was 4.1\% in the first pregnancy.
and 1.7% in later pregnancies. 19,540 of those who had pre-eclampsia in 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. Likewise, 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 11.4. Summary of studies that presents the risk of recurrence of pregnancy related hypertension in women with pre-eclampsia

<table>
<thead>
<tr>
<th>Study</th>
<th>No. Participants</th>
<th>GH (%)</th>
<th>PE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjartardottir 2006 Iceland</td>
<td>n=151</td>
<td>34(51)</td>
<td>13(20)</td>
</tr>
<tr>
<td>Brown 2007 Australia</td>
<td>n=239</td>
<td>13(31)</td>
<td>9(22)</td>
</tr>
<tr>
<td>Hargood 1991 Australia</td>
<td>n=19</td>
<td>53(10)</td>
<td>5(1)</td>
</tr>
<tr>
<td>Hernandez-Diaz 2009 Sweden</td>
<td>N=19,540</td>
<td>-</td>
<td>14.7(2,871)</td>
</tr>
<tr>
<td>Trogstad 2004 Norway</td>
<td>n=19,960</td>
<td>-</td>
<td>14(2,749)</td>
</tr>
<tr>
<td>Trogstad 2004 Norway; Singleton</td>
<td>n=325</td>
<td>-</td>
<td>7(23)</td>
</tr>
<tr>
<td>Campbell 1985 (Scotland)</td>
<td>n=279</td>
<td>30(84)</td>
<td>7.5(21)</td>
</tr>
<tr>
<td>Bass 2001 Denmark</td>
<td>n=8,401</td>
<td>-</td>
<td>16(1,344)</td>
</tr>
<tr>
<td>Mostello 2008 USA</td>
<td>n=6157</td>
<td>-</td>
<td>15(924)</td>
</tr>
<tr>
<td>Zhang 2001* USA</td>
<td>n=34</td>
<td>32(11)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Total:</td>
<td>N=55,105</td>
<td>25.9(187 / 722)</td>
<td>14.5(7975/55105)</td>
</tr>
</tbody>
</table>

Table 11.5 Summary of studies that presents the risk of recurrence of pregnancy related hypertension in women with pre-eclampsia

<table>
<thead>
<tr>
<th>1st pregnancy</th>
<th>Study</th>
<th>No. participants</th>
<th>GH (%)</th>
<th>PE (%)</th>
<th>HELLP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELLP</td>
<td>Sullivan 1994 USA</td>
<td>n=161</td>
<td>-</td>
<td>43(n=69)</td>
<td>19(n=31)</td>
</tr>
<tr>
<td></td>
<td>Sibai 1995 USA</td>
<td>n=212</td>
<td>9 (n=19)</td>
<td>24(n=51)</td>
<td>3(n=6)</td>
</tr>
<tr>
<td></td>
<td>Chames 2003 USA, Delivery &lt; 28 wks</td>
<td>n=62</td>
<td>-</td>
<td>55(n=34)</td>
<td>6(n=4)</td>
</tr>
<tr>
<td></td>
<td>Subtotal:</td>
<td>N=435</td>
<td>35.4(154/435)</td>
<td>9.4(41/435)</td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Adelusi 1986 Nigeria</td>
<td>n=64</td>
<td>-</td>
<td>-</td>
<td>16(n=10)</td>
</tr>
<tr>
<td></td>
<td>Sibai 1992 USA</td>
<td>n=366</td>
<td>-</td>
<td>22(n=80)</td>
<td>2(n=7)</td>
</tr>
<tr>
<td></td>
<td>Subtotal:</td>
<td>N=430</td>
<td>-</td>
<td>4%(17/430)</td>
<td></td>
</tr>
<tr>
<td>Severe pre-eclampsia</td>
<td>Sibai 1991 USA</td>
<td>n=169</td>
<td>-</td>
<td>65(n=110)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Rijn 2006 Netherlands</td>
<td>n=120</td>
<td>22.5(n=27)</td>
<td>25(n=30)</td>
<td>-</td>
</tr>
</tbody>
</table>
Effect of severity

Previous pregnancy with severe pre-eclampsia

One retrospective cohort study\[^{211}\] [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 yrs). The study showed that 65% (110/169) of subsequent pregnancies were complicated with pre-eclampsia (Table 11.6).

One large Swedish retrospective cohort study\[^{9}\] [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.

One retrospective cohort study\[^{212}\] [EL=2+] was conducted in the Netherlands and investigated the risk of recurrence of pre-eclampsia in subsequent pregnancy after early-onset pre-eclampsia (<34 weeks) in first pregnancy. 120 primiparous women were included (follow-up: average 6.3 yrs). 27 women (22.5%) developed gestational hypertension in the next pregnancy while 30 others (25.0%) developed pre-eclampsia (Table 11.6)

Women with previous HELLP syndrome

Three retrospective cohort studies\[^{206}-208\] [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 between 3% - 19%. Pooled results from the three studies showed an overall 9.4% (41/435) risk of developing HELLP syndrome. Recurrence of pre-eclampsia in subsequent pregnancies ranged from between 24% - 55%. Pooled results from the three studies revealed an overall risk of 35.4% (154/435) of developing pre-eclampsia. One study reported results on developing gestational hypertension in subsequent pregnancies and showed a risk of 9% (19/212) (Table 11.6).

Previous pregnancy with eclampsia

Two cohort studies\[^{209};210\] [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 retrospective cohort conducted in the USA and included 182 women who had eclampsia in the index pregnancy. These women had 366 subsequent pregnancies (follow up: average 7.2 yrs, range 3-13 yrs). 159 of those women were nulliparous (334 subsequent pregnancies) and 23 women were multiparous (32 subsequent pregnancies). The risk of recurrence of eclampsia in subsequent pregnancy was 1.9% (7/366), while risk of pre-eclampsia was 22% (80/366) (table.3)

The second study was a prospective cohort conducted in Nigeria which included 64 women who had eclampsia at index pregnancies. These women were followed up...
in next pregnancies. 10 women (15.6%) had a recurrence of eclampsia in next pregnancy (Table 11.6).

Pooled results from both studies showed an overall 4% (17/430) risk of developing eclampsia in subsequent pregnancies (Table 11.6).

Table 11.6. Summary of studies that presents the risk of recurrence of pregnancy related hypertension in women with HELLP syndrome, eclampsia, severe pre-eclampsia or pre-eclampsia before 34 weeks gestation.

<table>
<thead>
<tr>
<th>1st pregnancy</th>
<th>Study</th>
<th>No. participants</th>
<th>GH</th>
<th>PE</th>
<th>Eclampsia</th>
<th>HELLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HELLP</td>
<td>Sullivan 1994 USA</td>
<td>n=161</td>
<td>-</td>
<td>43% (n=69)</td>
<td>-</td>
<td>19% (n=31)</td>
</tr>
<tr>
<td></td>
<td>Sibai 1995 USA</td>
<td>n=212</td>
<td>9% (n=19)</td>
<td>24% (n=51)</td>
<td>-</td>
<td>3% (n=6)</td>
</tr>
<tr>
<td></td>
<td>Chames 2003 USA</td>
<td>n=62</td>
<td>-</td>
<td>55% (n=34)</td>
<td>-</td>
<td>6% (n=4)</td>
</tr>
<tr>
<td></td>
<td>Subtotal:</td>
<td>N=435</td>
<td>35.4% (154/435)</td>
<td>9.4% (41/435)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eclampsia</td>
<td>Adelusi 1986 Nigeria</td>
<td>n=64</td>
<td>-</td>
<td>-</td>
<td>16% (n=10)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sibai 1992 USA</td>
<td>n=366</td>
<td>22% (n=80)</td>
<td>2% (n=7)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal:</td>
<td>N=430</td>
<td>4% (17/430)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe pre-eclampsia</td>
<td>Sibai 1991 USA</td>
<td>n=169</td>
<td>-</td>
<td>65% (n=110)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Rijn 2006 Netherlands</td>
<td>n=120</td>
<td>22.5% (n=27)</td>
<td>25% (n=30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hernandez-Diaz 2009 Sweden (REF)</td>
<td>n=1,754</td>
<td>29% (n=509)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal:</td>
<td>N=2043</td>
<td>22.5% (27/120)</td>
<td>31.7% (649/2043)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Effect of gestational age

Previous pregnancy with gestational hypertension

One retrospective cohort study [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 – 1.41) or pre-eclampsia (OR=0.58, 95% CI 0.25 – 1.35).

Another retrospective cohort study [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 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 wks, versus 37-45 wks). 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 study [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 study[^205] [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 study[^198] [EL=2+] performed 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 – 3.20) or pre-eclampsia (OR=1.33, 95% CI 0.47 – 3.77).

**Previous pregnancy with HELLP syndrome**

One retrospective cohort study[^206] [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 patients with recurrent HELLP pregnancies were originally delivered at ≤ 32 weeks. Eleven of these 18 (61%) were also subsequently delivered at ≤ 32 weeks. Conversely, of the 18 patients who were originally delivered after 32 weeks, only two (11%) were subsequently delivered before 32 weeks.

**Evidence statement**

**Gestational hypertension**

In women with gestational hypertension in the index pregnancy, evidence from five retrospective cohort studies [EL=2+] showed a 32% (814/2,575) risk of developing gestational hypertension and 3% (85/2,575) risk of developing pre-eclampsia in subsequent pregnancy. One retrospective cohort study [EL 2+] (n=411) showed no differences between late and early onset of gestational hypertension in terms of risk of either gestational hypertension or pre-eclampsia recurrence in subsequent pregnancy. Another retrospective cohort study [EL 2+], however, showed an increase from 0% to 2.1% and from 21.4% to 29.1% in risk of developing pre-eclampsia and gestational hypertension in the second pregnancy if first pregnancy went to term (28-36 wks, versus 37-45 wks).

**Pre-eclampsia**

In women with pre-eclampsia in the index pregnancy, evidence from eight retrospective cohort studies [EL=2+] showed a 38.5% (278/722) risk of developing gestational hypertension and 14.5% (5,149/35,565) risk of developing pre-eclampsia in subsequent pregnancy.
The risk of recurrent 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 remains 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 65% (110/169) risk of developing pre-eclampsia in subsequent pregnancy.

Two studies have used gestation prior to 34 weeks at birth 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 is a 22.5% (27/120) 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+] showed a 9.4% (41/435) and 35.4%' (154/435) risk of developing HELLP syndrome and pre-eclampsia in subsequent pregnancy, respectively. One study showed a risk of 9% (19/212) of developing gestational hypertension in subsequent pregnancy.

Using eclampsia as a surrogate for severity, evidence from two cohort studies [EL 2+] showed a 4% (17/430) risk of developing eclampsia in subsequent pregnancies.

Examining the effect of gestational age at which pre-eclampsia develops one retrospective cohort study [EL=2+] (n=411) showed no differences between late and early onset of pre-eclampsia (≤34 wks gestation) in terms of risk of either gestational hypertension or pre-eclampsia recurrence in subsequent pregnancy. Another retrospective cohort study [EL=2+], however, showed an decrease from 13.0% to 6.8% and from 39.1% to 29.5% in risk of developing pre-eclampsia and gestational hypertension in the second pregnancy if first pregnancy went to term (28-36 wks, versus 37-45 wks). A large retrospective cohort study [EL=2+] (n=6,157) showed that 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.

Another complex retrospective cohort study showed that women who had eclampsia before 37 weeks had significantly higher incidences of pre-eclampsia in subsequent pregnancies as compared with women who had eclampsia≥37 weeks (43%≤ 30 wks; 32% 31-36 wks, 8% 37-41 wks, p<0.001). As for recurrence of eclampsia, no significant difference was detected.

GDG interpretation of the evidence

Gestational hypertension

There is consistent evidence across different populations that the risk to a woman who had gestational hypertension in her first pregnancy is on average 32% (range 16% - 47%) of recurrence of the condition in her next pregnancy and on average 3% (range 2% - 7%) chance of pre-eclampsia. This compares with the risk of 9% for gestational hypertension and 0.7% of pre-eclampsia when the first pregnancy was not complicated by hypertension.

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 as a result of differing definitions and methodologies between studies but the overall risk of pre-eclampsia in the subsequent pregnancy is on average 14.5% (range 0% - 16%). This risk is independent of which pregnancy is the first to be complicated by pre-eclampsia. The risk though
lower (8.7%) if a subsequent pregnancy is normotensive, remains elevated for the third pregnancy.

The risk of gestational hypertension in a subsequent pregnancy is on average 26% (range 13% - 53%).

There is evidence that the risk of recurrent pre-eclampsia is increased (range 22% - 65%) where the index pregnancy is complicated by severe disease (variously defined) or where disease of any severity presents before 34 weeks. The GDG feels that the risk under 34 weeks on average is around 25% but this appears to be nearer 40-60% where birth occurred at less than 28-30 weeks.

**Recommendations**

Inform women that if they had gestational hypertension in their first pregnancy, their risk of developing:

- gestational hypertension in their next pregnancy is on average 1 in 3 (32%)
- pre-eclampsia in their next pregnancy is 1 in 33 (3%).

Inform women that if they had pre-eclampsia in their first pregnancy, their risk of developing:

- gestational hypertension in their next pregnancy is 1 in 4 (26%)
- pre-eclampsia in their next pregnancy is around 1 in 7 (14.5%)
- pre-eclampsia in their next pregnancy is 1 in 4 (25%) if their pre-eclampsia was complicated by severe pre-eclampsia, HELLP syndrome or eclampsia and led to birth before 34 weeks, and 1 in 2 (55%) if it led to birth before 28-30 weeks.

**11.6 Inter-pregnancy interval and recurrence of hypertensive disorders of pregnancy**

**Clinical effectiveness**

One cohort study was identified \[EL=2+\] undertaken in Denmark between 1980 and 1994 to assess the risk or 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.
1. **Recommendations**

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

2. **11.7 Body mass index and recurrence of hypertensive disorders of pregnancy**

**Clinical effectiveness**

One retrospective cohort study [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 (Table 11.7).

<table>
<thead>
<tr>
<th>BMI</th>
<th>GA 20-32</th>
<th>GA 33-36</th>
<th>GA 37-47</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18.5</td>
<td>23.1%</td>
<td>14.3%</td>
<td>7.7%</td>
</tr>
<tr>
<td>18.5-24.9</td>
<td>29.3%</td>
<td>17.2%</td>
<td>9.5%</td>
</tr>
<tr>
<td>25-29.9</td>
<td>30.6%</td>
<td>25.3%</td>
<td>12.4%</td>
</tr>
<tr>
<td>30-34.9</td>
<td>32.4%</td>
<td>25.0%</td>
<td>17.5%</td>
</tr>
<tr>
<td>≥35.0</td>
<td>40.0%</td>
<td>29.1%</td>
<td>17.8%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>14.7%</td>
<td></td>
</tr>
</tbody>
</table>

**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).
12 References, abbreviations and glossary

12.1 References


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12.2 Abbreviations

1. ACE: angiotensin-converting enzyme
2. ACOG: American College of Obstetricians and Gynecologists
3. ACR: albumin creatinine ratio
4. ALT: alanine aminotransferase
5. ANC: antenatal care
6. APCR: activated protein C resistance
7. ARB: angiotensin receptor blocker
8. ARDS: adult respiratory distress syndrome
9. AST: aspartate aminotransferase
10. b.i.d: twice daily
11. BMI: body mass index
12. BPD: bronchopulmonary dysplasia
13. BPP: biophysical profile
14. CH: chronic hypertension
15. CI: confidence interval
16. CS: caesarean section
17. CTG: cardiotocograph
18. CVD: cardiovascular disease
19. dL: decilitre
20. EL: evidence level
21. ESRD: end stage renal disease
22. FDA: Federal Drug Administration
23. g.: gram
24. GA: gestational age
25. Hg: mercury
26. HDZ: hydralazine
27. Hg: mercury
28. Abruption/Abruptio placenta: Separation of the placenta before the baby is born
29. Absent end diastolic velocities: Found during Doppler evaluation of umbilical artery and implying placental disease
30. ACE inhibitors: Angiotensin-converting enzyme inhibitors – an antihypertensive
31. APCR: Activated protein C resistance – see thrombophilia
32. Protein C / Protein S: See thrombophilia
33. Acetylsalicylic acid: Aspirin
34. Alanine amnion transferase (ALAT or ALT): A liver enzyme raised in presence of liver damage
35. Amniotic Fluid Index (AFI): A method of amniotic fluid measurement by adding the biggest pools in each of the 4 quarters of the uterus
36. Albuminuria: Albumin is a type of protein in the blood which appears in urine in the presence of renal damage
37. Antenatal day unit: A unit established to undertake a variety of pregnancy assessments and so reduce the need for admission to hospital
38. Anticardiolipins: Antibodies which are formed against the cellular component cardiolipin
39. Vitamins C and E are regarded as potent anti-oxidants
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid syndrome</td>
<td>Condition where have anticardiolipin antibodies and history of blood clots,/miscarriage or poor pregnancy outcomes</td>
</tr>
<tr>
<td>Antiplatelet agents</td>
<td>Drugs that change the way platelets work</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>One of the thrombophilies (see later), and one of the most severe types</td>
</tr>
<tr>
<td>Apgar scores</td>
<td>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</td>
</tr>
<tr>
<td>ARDS</td>
<td>Adult respiratory distress syndrome</td>
</tr>
<tr>
<td>ARBs</td>
<td>Angiotensin receptor blocking agents - antihypertensives</td>
</tr>
<tr>
<td>Atenolol</td>
<td>A beta-blocker antihypertensive</td>
</tr>
<tr>
<td>Autoimmune disease</td>
<td>A disease in which the body raises antibodies against itself</td>
</tr>
<tr>
<td>Automated dipstick test/ reading</td>
<td>A method of testing for protein in the urine using a machine</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>See atenolol</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Excretion product from the liver - in excess leads to jaundice</td>
</tr>
<tr>
<td>Biophysical Profile (BPP)</td>
<td>A method of fetal assessment which includes fetal movement, fetal breathing, fetal muscle tone, amniotic fluid volume and fetal cardiotocography</td>
</tr>
<tr>
<td>Body mass index</td>
<td>Measure of body build estimated from the individuals height and weight</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>A local anaesthetic used in regional anaesthesia</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Types of antihypertensives</td>
</tr>
<tr>
<td>Cardiotocograph (CTG)</td>
<td>A continuous recording of the fetal heart rate</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>Hypertension that already exists - it can be primary (no obvious cause) or secondary to an underlying condition, such as renal disease</td>
</tr>
<tr>
<td>Clean catch specimen</td>
<td>A method of collecting urine to reduce contamination</td>
</tr>
<tr>
<td>Clonus</td>
<td>A muscle condition associated with hyper-reflexia and found in severe pre-eclampsia</td>
</tr>
<tr>
<td>Coagulation</td>
<td>Concerned with blood clotting</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Where the blood clotting is abnormal; blood does not clot as well</td>
</tr>
<tr>
<td>Co-morbidities</td>
<td>Situation in which a number of different conditions co-exist</td>
</tr>
<tr>
<td>Congenital malformation</td>
<td>An abnormality present at birth</td>
</tr>
<tr>
<td>Converting enzyme DD</td>
<td>A rare genetic disorder associated with absent converting enzyme and increased tendency to thrombosis</td>
</tr>
<tr>
<td>Convulsions</td>
<td>Fits, seizures</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Hormones produced by the adrenal gland and used to help mature a baby’s slungs</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Chemical excreted from the kidney that is used to assess how the kidney is working.</td>
</tr>
<tr>
<td>Crystallloid</td>
<td>A water soluble substance i.e. salt</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>A type of anticoagulant injection used to prevent blood clots</td>
</tr>
<tr>
<td>Day care evaluation</td>
<td>See antenatal care unit</td>
</tr>
<tr>
<td>Decelerations</td>
<td>Slowing of the fetal heart rate</td>
</tr>
<tr>
<td>Dinoprostone</td>
<td>A prostaglandin</td>
</tr>
<tr>
<td>Diprydamole</td>
<td>An antiplatelet agent</td>
</tr>
<tr>
<td>Dipstick</td>
<td>An impregnated stick for testing urine</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Drugs which encourage the kidneys to make urine, sometimes called ‘water tablets’</td>
</tr>
<tr>
<td>Doppler velocimetry</td>
<td>A method of assessing both uterine and umbilical blood velocities, which helps work out if placenta working well</td>
</tr>
<tr>
<td>Ductus Arteriosus</td>
<td>The blood vessel located between the pulmonary artery and the aorta which is open in fetal life but which closes soon after birth</td>
</tr>
<tr>
<td>Eclampsia/eclamptic</td>
<td>A convulsive condition which arises from pre-eclampsia</td>
</tr>
<tr>
<td>Egger test</td>
<td>A statistical test to see if there is bias in results</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>Constituents of the blood which include sodium, potassium and chloride</td>
</tr>
<tr>
<td>Embryo-fetal adverse outcome</td>
<td>Loss or damage of either an embryo (usually as miscarriage) or as a fetus (usually as stillbirth, abnormality or growth restriction)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>ACE inhibitor – a blood pressure lowering drug</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Adrenaline</td>
</tr>
<tr>
<td>Epidural</td>
<td>A method of pain relief involving placing a plastic tube in the back and giving drugs through it to stop pain</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>Pain in the upper central part of the abdomen</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Beta-blocker antihypertensive</td>
</tr>
<tr>
<td>Established pre-eclampsia</td>
<td>Definite pre-eclampsia</td>
</tr>
<tr>
<td>Factor V Leiden</td>
<td>See thrombophilies</td>
</tr>
<tr>
<td>Factor II 20210A variant</td>
<td>Ditto</td>
</tr>
<tr>
<td>Fetal Biometry</td>
<td>Measurement of the fetus by ultrasound usually to include head, abdomen and femur length</td>
</tr>
<tr>
<td>Fetal growth restriction/ IUGR</td>
<td>A condition in which the fetus fails to meet its growth potential; a small baby who is not growing</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>A morphine – based drug for pain relief</td>
</tr>
<tr>
<td>Focal neurological deficit</td>
<td>Clinical evidence of localised nerve damage usually involving the brain</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>A fetus who may be lacking in oxygen, usually diagnosed by the presence of an abnormal CTG</td>
</tr>
<tr>
<td>Foley catheter</td>
<td>A type of bladder catheter</td>
</tr>
<tr>
<td>Full blood count</td>
<td>Usually haemoglobin which measures degree of anaemia, white cell which tells about infection and platelet counts which</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>FVL homozygous</td>
<td>See thrombophilias</td>
</tr>
<tr>
<td>Genotype/ specific genotype</td>
<td>The genetic makeup of an individual</td>
</tr>
<tr>
<td>Gestational hypertension</td>
<td>New hypertension that starts after 20 weeks of pregnancy and where there is no proteinuría</td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Measures anaemia</td>
</tr>
<tr>
<td>Haematuria</td>
<td>Blood in the urine</td>
</tr>
<tr>
<td>Haematological evaluation</td>
<td>Tests of the blood</td>
</tr>
<tr>
<td>Haemodynamic response</td>
<td>Term used to describe the heart and blood vessel response usually to treatment</td>
</tr>
<tr>
<td>Haemolysis</td>
<td>Breakdown of red blood cells</td>
</tr>
<tr>
<td>HDU</td>
<td>High Dependency Unit</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Haemolysis, elevated liver enzymes, low platelets – a type of severe pre-eclampsia</td>
</tr>
<tr>
<td>Heterozygous</td>
<td>State of different genes at the same locus on the chromosome</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>A smooth muscle relaxant antihypertensive usually only used where severely high blood pressure</td>
</tr>
<tr>
<td>Hyperbilirubinaemia</td>
<td>Excessive bilirubin in the blood</td>
</tr>
<tr>
<td>Hyperglycaemic</td>
<td>Excessive glucose in the blood</td>
</tr>
<tr>
<td>Hyperhomocysteinaemia</td>
<td>See thrombophilias</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>Excessive potassium in the blood</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Excessive lipids in the blood</td>
</tr>
<tr>
<td>Hyperreflexia</td>
<td>Increased reflexes for example knee jerk</td>
</tr>
<tr>
<td>Hypertension</td>
<td>High blood pressure</td>
</tr>
<tr>
<td>Hypertension (mild, moderate, severe)</td>
<td>See introduction for definitions used</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Low blood pressure</td>
</tr>
<tr>
<td>Infusion pump</td>
<td>A pump used to help fluids into a patient usually via a vein</td>
</tr>
<tr>
<td>Intracranial pressure</td>
<td>Pressure within the skull</td>
</tr>
<tr>
<td>Intubation</td>
<td>Technique whereby a tube is placed in the patient windpipe to aid breathing or for anaesthetic purposes</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>Usually term used to describe coronary heart disease (heart attack or angina)</td>
</tr>
<tr>
<td>ITU</td>
<td>Intensive Therapy Unit</td>
</tr>
<tr>
<td>Labetalol</td>
<td>A blood pressure treatment that has beta and alpha blocker actions</td>
</tr>
<tr>
<td>Lactic dehydrogenase (LDH)</td>
<td>Enzyme released by tissue damage</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td>Type of fatty acid</td>
</tr>
<tr>
<td>Low birthweight</td>
<td>A term used to define babies weighing less than 2.5 kg</td>
</tr>
<tr>
<td>Lupus anticoagulants</td>
<td>Type of auto-antibodies that increase the risk of blood clots</td>
</tr>
<tr>
<td>Lytic cocktail</td>
<td>A mixture of pethidine, chlorpromazine and promethazine used to prevent fits in pre-eclampsia/eclampsia</td>
</tr>
<tr>
<td>MgSO4</td>
<td>Magnesium sulphate</td>
</tr>
</tbody>
</table>

Hypertension in pregnancy: full guideline DRAFT (September 2009) Page 214 of 244
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical ventilation</td>
<td>Assisted ventilation</td>
</tr>
<tr>
<td>Meperidine</td>
<td>Opioid drug for pain relief. Better known as Demerol</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Centrally acting drug that lowers blood pressure</td>
</tr>
<tr>
<td></td>
<td>Very small amounts of the protein albumin in the urine. It is used as a test of kidney function.</td>
</tr>
<tr>
<td>Microalbumin</td>
<td></td>
</tr>
<tr>
<td>Multi-gravid</td>
<td>More than 1 pregnancy</td>
</tr>
<tr>
<td>Multiparous</td>
<td>More than 1 pregnancy resulting in a stillbirth after 24 weeks or a live birth</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>Pregnancy with more than one fetus</td>
</tr>
<tr>
<td>MTHFR homozygous</td>
<td>See thrombophilias</td>
</tr>
<tr>
<td>Naloxone</td>
<td>A drug which reverses the respiratory depressant effects of morphine-based drugs</td>
</tr>
<tr>
<td>NEC</td>
<td>Necrotising enterocolitis</td>
</tr>
<tr>
<td>Neonate</td>
<td>A baby between 7 and 28 days of life</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal Intensive Care Unit</td>
</tr>
<tr>
<td>Nitric oxide agents/ donors/ precursors</td>
<td>Drugs that cause blood vessels to dilate</td>
</tr>
<tr>
<td>Non-reassuring fetal heart rate (FHR)</td>
<td>A classification of the fetal heart rate that means possible fetal distress. It can sometimes mean abnormal.</td>
</tr>
<tr>
<td>Normotensive</td>
<td>Normal blood pressure</td>
</tr>
<tr>
<td>Nulliparous/nulliparity</td>
<td>First pregnancy</td>
</tr>
<tr>
<td>Obesity</td>
<td>Overweight defined by BMI or by weight</td>
</tr>
<tr>
<td>Oedema</td>
<td>Waterlogging of the tissue; swelling</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>Reduced amounts of amniotic fluid around the fetus</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Reduced urine production. Can be defined as per day or per hour.</td>
</tr>
<tr>
<td>Opioid</td>
<td>Morphine-based drugs</td>
</tr>
<tr>
<td>Oxytocin augmentation</td>
<td>Use of the drug oxytocin to stimulate labour that has already started</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Irregular heart beat felt by the patient as flutters</td>
</tr>
<tr>
<td>Parenteral</td>
<td>Route of administration - usually via the vein or muscle</td>
</tr>
<tr>
<td>Patent Ductus Ateriosus</td>
<td>See duc tus arteriosus</td>
</tr>
<tr>
<td>Perinatal</td>
<td>Usually defined as a period from 24 weeks gestation to 7 days after birth</td>
</tr>
<tr>
<td>pH scale</td>
<td>A logarithmic scale used to assess acidity</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>See abruption</td>
</tr>
<tr>
<td>Plasma</td>
<td>The fluid, non-cellular part of the blood</td>
</tr>
<tr>
<td>Platelets</td>
<td>Small cellular fragments responsible for blood clotting</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>An index of fat content usually in babies</td>
</tr>
<tr>
<td>Positive roll-over test</td>
<td>An archaic test of risk of pre-eclampsia</td>
</tr>
<tr>
<td>Post-partum haemorrhage</td>
<td>A loss from the genital tract after birth of &gt;500mls</td>
</tr>
<tr>
<td></td>
<td>New hypertension after 20 weeks of pregnancy where there is significant proteinuria (more than 300 mg in a 24-hour urine collection).</td>
</tr>
<tr>
<td>Pre-eclampsia/ PET</td>
<td></td>
</tr>
</tbody>
</table>
Prematurity

Pre-term birth/ delivery

Pregnancy-induced hypertension

Primiparous/ primiparity / primigravida

Prognosis

Promethazine

Protein C deficiency

Protein S deficiency

Proteinuria

Prothrombin

Pulmonary oedema

Respiratory distress syndrome

Retrolental Fibroplasia

RPE

SCBU

Secondary care setting

Seizure

Serum

Uric acid

Severe hypertension

Severe pre-eclampsia

Single Deepest Vertical Pool (SVDP)

Significant proteinuria

SLE

Small for gestational age

Spontaneous vaginal birth

Spot protein creatinine ratio

Stillbirth

Thrombocytopaenia

Thromboembolism

Thrombophilia

Tramadol

Transaminases

Umbilical artery Doppler scan

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 thrombophilias

Protein S deficiency

ditto

Proteinuria

Protein in the urine – see albuminuria

Prothrombin

A protein associated with blood clotting

Pulmonary oedema

A condition of the newborn when the lungs are immature because they are not producing enough of a substance called surfactant

Respiratory distress syndrome

A eye condition associated with prematurity

Retrolental Fibroplasia

A scale for setting intensity of exercise

SCBU

Special care baby unit

Secondary care setting

Hospital based care

Seizure

Fit

Serum

Fluid which exudes from clotted plasma

Uric acid

A blood analyte which can be increased if the kidneys are not working well enough

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

Usualy defined as being below a certain birth weight for weeks of pregnancy. Can be written as less than 5th or 10th.

Small for gestational age

Spontaneous vaginal birth

A one off test for urine protein excretion

Spot protein creatinine ratio

A baby born dead after 24 weeks gestation

Stillbirth

A reduced number of platelets in the blood

Thrombocytopaenia

A blood clot in the circulation

Thromboembolism

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

Thrombophilia

A morphine-like analgesic

Tramadol

Liver enzymes which are elevated when there is cellular damage in the liver

Transaminases

A technique to estimate blood velocity in
<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual scotomata</td>
<td>A condition in which there are blind areas within the individual's visual fields</td>
</tr>
<tr>
<td>Xylocaine</td>
<td>Local anaesthetic</td>
</tr>
</tbody>
</table>
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


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:


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 24 August 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
James Walker
Personal pecuniary interests: Spin-out companies studying predictors of pre-eclampsia - none operating commercially at present
Personal non-pecuniary interests: Action on Pre-eclampsia; International Society for the Study of Hypertension in Pregnancy
Stephen Walkinshaw
No interests declared
David Williams
No interests declared

NCC-WCH staff and contractors

M Qutayba Almerie
No interests declared
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

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

CISTers

Cochrane Pregnancy & Childbirth Group

Commission for Social Care Inspection

Connecting for Health

Conwy and Denbighshire NHS Trust

Cytyc UK Limited

Department of Health

Department of Health, Social Security and Public Safety of Northern Ireland

Derbyshire Mental Health Services NHS Trust

Dudley Group of Hospitals NHS Trust

East & North Herts PCT & West Herts PCT

Health Commission Wales

Healthcare Commission
Infermed Ltd
J BOL Ltd
Kingston Hospital NHS Trust
Kirklees Primary Care Trust
La Leche League GB
Leeds PCT
Leeds Teaching Hospitals NHS Trust
Liverpool Women’s NHS Foundation Trust
Liverpool Women’s NHS Trust
Luton & Dunstable Hospital NHS Foundation Trust
Medicines and Healthcare Products Regulatory Agency (MHRA)
Mid and West Regional Maternity Services Liaison Committee
National Childbirth Trust
National Patient Safety Agency (NPSA)
National Public Health Service - Wales
National Screening Committee
National Treatment Agency for Substance Misuse
NHS Direct
NHS Plus
NHS Purchasing & Supply Agency
NHS Quality Improvement Scotland
North Cheshire Hospitals
North Tees and Hartlepool Acute Trust
North Yorkshire and York PCT
Northern Lincolnshire and Goole Hospitals NHS Foundation Trust
Northumbria Healthcare NHS Foundation Trust
Obstetric Anaesthetists Association
P.M.S (Instruments) Ltd
 Partnerships for Children, Families, Women and Maternity
PERIGON Healthcare Ltd
PRIMIS+
Programme development Group in Maternal and Child Nutrition
RCM Consultant Midwives Group
Roche Diagnostics
Royal Brompton & Harefield NHS Trust
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health
Royal College of Pathologists
Royal College of Physicians of London
Royal College of Physicians of London
Royal Society of Medicine
SACAR
Salford Royal Hospitals Foundation NHS Trust
Sandwell & West Birmingham Hospitals NHS Trust
Sandwell PCT
Sanofi-Aventis
Scottish Intercollegiate Guidelines Network (SIGN)
Sheffield PCT
Sheffield Teaching Hospitals NHS Foundation Trust
Sherwood Forest Hospitals NHS Foundation Trust
Social Care Institute for Excellence (SCIE)
Solvay Healthcare Limited
Southampton University Hospital Trust
Syner-Med Pharmaceutical Products Ltd
Takeda UK
Tameside Acute Trust
The British Dietetic Association
The British Renal Society
The Renal Association
UCLH NHS Foundation Trust
United Lincolnshire Hospitals NHS Trust
University College London Hospitals NHS Foundation Trust
University of Leicester (The Infant Mortality & Morbidity Studies)
Wellbeing of Women
Welsh Assembly Government
Welsh Scientific Advisory Committee
Wiltshire PCT
Wirral University Teaching Hospital NHS Foundation Trust
Worthing and Southlands Hospital
York Hospital NHS Foundation Trust
Yorkshire and the Humber LS
Appendix D

Clinical questions

- What interventions (including lifestyle advice) are effective at reducing the incidence of hypertensive disorders in pregnancy?
- What advice/interventions should be offered to women with chronic hypertension planning to become pregnant?
- What interventions for chronic hypertension are effective at improving outcomes for women and infants?
- What investigations, monitoring and advice should take place when gestational hypertension is diagnosed?
- What interventions are effective in improving outcomes for women and infants 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 intracranial 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 foetus, 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 vasmotor 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 methylpapa), 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, hyperbilirubinemia, 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%)
- Polycythemia (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 matemal 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 see 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 were no fetal or neonatal complications were found.

Michigan Medicaid surveillance study – 52 infants exposed in 1st trimester – 3 (5.8%) major birth defects (2 expected).

A study compared 101 hypertensive pregnant women taking metoprolol (n=57) or combined with hydralazine (n=44) to 97 women taking hydralazine alone. Mean gestation was 34.1 weeks (13-41 weeks) for the metoprolol group and 32.5 weeks (12-40 weeks). The metoprolol group experienced a lower rate of perinatal mortality (2% versus 8%) and a lower incidence of IUGR (11.7% versus 16.3%). No signs or symptoms of 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 liked 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, C-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 hyperbilirubinemia.

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

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

See chlorothiazide

A study reported 1011 women who received 5mg bendrofluazide 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 patients treated for oedema (drug not stated / hypertensive patients 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
Cyclopenthiazide
See chlorothiazide
Indapamide (Limited human data) (Bm*)
Michigan Medicaid surveillance study – 46 infants exposed in 1st trimester to indapamide – 3 (6.5%) major birth defects (2 expected).
Metolazone (Limited human data – Probably compatible) (Bm*)
See chlorothiazide
Xipamide
No information

Loop

Furosemide (Human data suggest low risk) (Cm*)
Crosses the placenta
Michigan Medicaid surveillance study – 350 infants exposed in 1st trimester – 18 (5.1%) major birth defects (15 expected). May support an association with furosemide and congenital defects (hypospadias), but other factors (mother’s disease, concurrent drug use and chance) may be involved.
Furosemide has been used in the 2nd and 3rd trimesters for oedema, hypotension and toxaemia without fetal or newborn adverse effects.

Vasodilator drugs
Hydralazine (Human data suggest risk in 3rd trimester) (Cm)
Hydralazine crosses the placenta leading to concentrations equal or greater than that of the mother in the neonate.
No reports linking hydralazine with congenital defects were located.
Collaborative Perinatal Project (CPP) – 8 infant exposures in 1st trimester / 136 infant exposures throughout pregnancy – no abnormalities found with 1st trimester use. 8 (5.8%) infants had defects when used in the 2nd and 3rd trimesters which is higher than expected, however the severity of the maternal condition may be responsible for this.
Michigan Medicaid surveillance study – 40 infants exposed in 1st trimester – 1 (2.5%) major birth defects (2 expected).
Neonatal thrombocytopenia and bleeding secondary to hydralazine ingestion throughout the 3rd trimester have been reported in 3 infants. This however may have been due to maternal hypertension.
Bosentan (No human data) (Xm)
Bosentan and its metabolites are expected to cross the placenta
No reports in human pregnancy were located.
Diazoxide (Human data suggest risk in 3rd trimester) (Cm)
Diazoxide readily crossed the placenta reaching fetal levels similar to that of the mother.
In one study the decrease in maternal blood pressure was sufficient to produce a state of clinical shock and endanger placental perfusion. Transient fetal bradycardia has been reported in other studies following a rapid, marked decrease in maternal blood pressure. Fatal maternal hypotension has also been reported.
Rather than rapid IV boluses, small IV boluses at frequent intervals have successfully controlled maternal blood pressure without producing fetal toxicity.

Diazoxide is a potent relaxant of smooth muscle and may inhibit uterine contractions if given during labour (dose dependant effect); augmentation of labour with oxytocin may be required.

Neonatal hyperglycaemia has been reported after IV diazoxide use in the mother and can persist for 24-72 hours post delivery.

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

## Safety of commonly used antihypertensive drugs during breastfeeding

<table>
<thead>
<tr>
<th>Drug Class / Name</th>
<th>M:P ratio</th>
<th>Relative infant dose</th>
<th>Reported paediatric concerns</th>
<th>Monitoring</th>
<th>Comments</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thiazide diuretics</strong></td>
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<tr>
<td>Bendrofluazide</td>
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<td></td>
<td>Amount too small to be harmful(^{236})</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Large doses may suppress lactation(^{236,238})</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>American academy of paediatrics classifies as compatible with breastfeeding(^{238})</td>
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<tr>
<td>Chlortalidone</td>
<td>0.062</td>
<td>15.5%(^{236})</td>
<td>Nil</td>
<td></td>
<td>Amount too small to be harmful(^{236})</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Long half life and may accumulate in milk(^{236})</td>
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<td></td>
<td></td>
<td>Highly plasma protein bound(^{239})</td>
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<td>Large doses may suppress lactation(^{236,237})</td>
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<tr>
<td>Cylopenthiazide</td>
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<td>Amount too small to be harmful(^{236})</td>
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<td></td>
<td>Large doses may suppress lactation(^{236})</td>
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<tr>
<td>Indapamide</td>
<td></td>
<td></td>
<td>Milk supply(^{237})</td>
<td></td>
<td>No reports of exposure via breast milk(^{237})</td>
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<td></td>
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<td></td>
<td>Volume depletion(^{237})</td>
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<td>Manufacturer suggests avoid(^{236})</td>
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<td></td>
<td>May suppress lactation(^{238})</td>
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<tr>
<td>Metolazone</td>
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<td>Amount too small to be harmful(^{236})</td>
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<td>Large doses may suppress lactation(^{236})</td>
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<tr>
<td><strong>Loop diuretics</strong></td>
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<tr>
<td>Furosemide</td>
<td>0.5-0.82</td>
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<td>Nil(^{237})</td>
<td></td>
<td>Amount too small to be harmful(^{236})</td>
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<td></td>
<td>Very unlikely that quantity transmitted in breast milk would produce effects in a nursing infant((relatively high doses used therapeutically in children))^{237}</td>
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<td>Large doses may suppress lactation(^{236,237})</td>
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<td>Torasemide</td>
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<td>No reports of exposure through breast milk(^{237})</td>
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<td>High plasma protein binding(^{237})</td>
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<td></td>
<td>May reduce milk supply(^{237})</td>
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<td><strong>Other diuretics</strong></td>
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<td>Amiloride</td>
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<td>No human exposure via breast milk reported(^{234})</td>
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<td>Passage into milk is expected(^{234})</td>
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<td><strong>Beta-blockers</strong></td>
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<tr>
<td>Propranolol</td>
<td>0.2-1.54</td>
<td>0.28%(^{237})</td>
<td>Nil(^{237})</td>
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<td>Monitor for symptoms of beta-</td>
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<td></td>
<td>Amount in breast milk low(^{237})</td>
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<td>Circulatory problems and</td>
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<tr>
<td>Drug</td>
<td>Concentration</td>
<td>Comments</td>
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<tr>
<td>Acebutolol</td>
<td>0.33-1.65</td>
<td>Hypertension, bradycardia, tachycardia and drowsiness 237, 238</td>
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<tr>
<td></td>
<td>(average 0.5)</td>
<td>American academy of paediatrics classifies as compatible with breastfeeding 238</td>
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<tr>
<td></td>
<td>0.49% 239</td>
<td>Possible toxicity due to beta-blockade but amount of most beta-blockers present in milk too small to affect infant 238</td>
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<tr>
<td></td>
<td>3.6% 237</td>
<td>Long term effects on infant not known 238</td>
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<tr>
<td></td>
<td>Symptoms of beta-blockade have been observed (Hypotension, bradycardia, tachycardia and drowsiness) 237, 238</td>
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<tr>
<td></td>
<td>Symptoms of beta-blockade 238</td>
<td>Hypoglycaemia reported in breastfeeding infants 239</td>
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<tr>
<td></td>
<td>Low protein binding and primary excretion via kidneys 239</td>
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<tr>
<td></td>
<td>Some authors have failed to detect atenolol in breast milk 237, 238</td>
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<tr>
<td></td>
<td>Possible significant transfer to baby and accumulation in premature infants 236, 238, 239</td>
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<tr>
<td>Atenolol</td>
<td>1.5-6.0 237</td>
<td>One reported case of bradycardia, cyanosis and hypothermia required hospitalisation 237, 238</td>
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<tr>
<td></td>
<td>6.6% 237</td>
<td>Hypertension, bradycardia, tachycardia and drowsiness 237, 238</td>
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<tr>
<td></td>
<td>Symptoms of beta-blockade 238</td>
<td>Low protein binding and primary excretion via kidneys 239</td>
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<tr>
<td></td>
<td>Some authors have failed to detect atenolol in breast milk 237, 238</td>
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<td></td>
<td>Possible significant transfer to baby and accumulation in premature infants 236, 238, 239</td>
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<tr>
<td></td>
<td>No reports of use in lactating mothers 238</td>
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<tr>
<td>Bisoprolol</td>
<td>Nil 237</td>
<td>Hypertension, bradycardia, other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>Nil 237, 238</td>
<td>No reports of use in lactating mothers 238</td>
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<tr>
<td></td>
<td>Hypotension and apnoea 237</td>
<td>No human data available 237, 238</td>
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<tr>
<td></td>
<td>Hypotension, bradycardia, other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>Only small quantities excreted into breast milk 237, 238</td>
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<tr>
<td></td>
<td>Concentrated in breast milk – with milk levels approx 237 times that of maternal plasma 237</td>
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<tr>
<td></td>
<td>Maternal plasma levels are small and so infant dose remains low 237</td>
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<tr>
<td>Labetalol</td>
<td>0.2-1.5 238</td>
<td>Hypertension, weakness, bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>0.5% 237</td>
<td>Hypertension and apnoea 237</td>
<td>Low half life 237</td>
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<tr>
<td></td>
<td>Nil 237, 238</td>
<td>Secreted into breast milk in moderately high amounts, possible significant transfer to baby and accumulation in premature infants 231, 237</td>
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<td></td>
<td>Hypotension, weakness, hypoglycaemia, sedation and depression 238</td>
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<td>Only small quantities excreted into breast milk 237, 238</td>
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<tr>
<td></td>
<td>Bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>Excreted into breast milk, amounts likely insignificant for the infant 238</td>
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<tr>
<td>Metoprolol</td>
<td>3-3.7 237</td>
<td>Hypertension, weakness, bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>1.4% 237</td>
<td>Hypertension, bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>Nil 237, 238</td>
<td>Concentrated in breast milk – with milk levels approx 237 times that of maternal plasma 237</td>
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<td></td>
<td>Maternal plasma levels are small and so infant dose remains low 237</td>
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<tr>
<td>Nadolol</td>
<td>4.6 237</td>
<td>Hypertension, weakness, bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>4.6% 237</td>
<td>Symptoms of beta-blockade 238</td>
<td>Long half life 237</td>
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<tr>
<td></td>
<td>Nil 237, 238</td>
<td>Secreted into breast milk in moderately high amounts, possible significant transfer to baby and accumulation in premature infants 231, 237</td>
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<td></td>
<td>Hypertension, weakness, hypoglycaemia, sedation and depression 238</td>
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<td></td>
<td>Only small quantities excreted into breast milk 237, 238</td>
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<td></td>
<td>Bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>Excreted into breast milk, amounts likely insignificant for the infant 238</td>
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<tr>
<td>Oxprenolol</td>
<td>0.14-0.45 238</td>
<td>Bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>Nil 238</td>
<td>Excreted into breast milk, amounts likely insignificant for the infant 238</td>
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<tr>
<td>Pindolol</td>
<td>Bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td></td>
<td>Manufacturer states present in breast milk 238</td>
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<td></td>
<td>No reports of exposure though breast milk reported 238</td>
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<tr>
<td>Timolol</td>
<td>0.8-0.83 238</td>
<td>Hypertension, weakness, hypoglycaemia, sedation and depression 238</td>
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<tr>
<td></td>
<td>1.1% 237</td>
<td>Hypertension, weakness, hypoglycaemia, sedation and depression 238</td>
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<tr>
<td></td>
<td>Nil 237, 238</td>
<td>Levels in breast milk unlikely to be significant 237</td>
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<tr>
<td></td>
<td>Hypertension, weakness, hypoglycaemia, sedation and depression 238</td>
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<tr>
<td></td>
<td>Excreted into breast milk, amounts likely insignificant for the infant 238</td>
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<td></td>
<td>Bradycardia and other symptoms of beta-blockade 238</td>
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<tr>
<td>Alpha blockers</td>
<td></td>
<td>Hypoglycaemia reported in breastfeeding infants 239</td>
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<tr>
<td>Doxazosin</td>
<td>Nil 238</td>
<td>No reports of use in human lactation 234</td>
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<tr>
<td>Prazosin</td>
<td>Nil 238</td>
<td>No reports of use in human lactation 234</td>
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<td></td>
<td>Hypoglycaemia reported in breastfeeding infants 239</td>
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<td></td>
<td>Amount probably too small to be harmful 238</td>
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</table>
### ACE Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration in Breast Milk</th>
<th>Hypotension</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>0.032 - 0.012 (237, 238)</td>
<td>Nil</td>
<td>Manufacturer suggests avoid (236)</td>
</tr>
<tr>
<td>Enalapril</td>
<td>0.17% (237)</td>
<td>Nil</td>
<td>Amount probably too small to be harmful (236, 238)</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Nil</td>
<td>29%</td>
<td>Barely detectable levels present in breast milk (no values reported) (237)</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>Nil</td>
<td></td>
<td>Manufacturer suggests avoid (236)</td>
</tr>
<tr>
<td>Moexipril</td>
<td>No reports of use during human lactation (238)</td>
<td>Excretion into human breast milk should be expected (238)</td>
<td>Manufacturer suggests avoid (238)</td>
</tr>
<tr>
<td>Perindopril</td>
<td>No reports of use during human lactation (238)</td>
<td>Excretion into human breast milk should be expected (including its active metabolite) (238)</td>
<td>Manufacturer suggests avoid (238)</td>
</tr>
<tr>
<td>Quinapril</td>
<td>0.12 (237, 238)</td>
<td>Nil</td>
<td>Present in breast milk (239)</td>
</tr>
<tr>
<td>Ramipril</td>
<td>0.25% (237)</td>
<td>Nil</td>
<td>Amounts available in breast milk clinically insignificant (238)</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>No reports of use during human lactation (238)</td>
<td>Excretion into human breast milk should be expected (238)</td>
<td>Manufacturer suggests avoid (238)</td>
</tr>
</tbody>
</table>

### Angiotensin II receptor blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Concentration in Breast Milk</th>
<th>Hypotension</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>No reports of use during human lactation (238)</td>
<td>Excretion into human breast milk should be expected (238)</td>
<td>Manufacturer suggests avoid (238)</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>No reports of use during human lactation (238)</td>
<td>Excretion into human breast milk should be expected (238)</td>
<td>Manufacturer suggests avoid (238)</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>No reports of use during human lactation (238)</td>
<td>Excretion into human breast milk should be expected (238)</td>
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<tr>
<td>Antihypertensives</td>
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</tr>
<tr>
<td>Manufacturer suggests avoid</td>
<td>No reports of use during human lactation</td>
<td>Excretion into human breast milk should be expected</td>
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<tr>
<td>Losartan</td>
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<tr>
<td>Olmesartan</td>
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<td>Telmesartan</td>
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<tr>
<td>Valsartan</td>
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<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Amlodipine</td>
<td>Nil</td>
<td>No reports of use during human lactation</td>
<td>Excretion into human breast milk should be expected</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>0.2-0.92 &lt;br&gt; 13</td>
<td>0.8%</td>
<td>Hypotension, bradycardia</td>
</tr>
<tr>
<td>Felodipine</td>
<td></td>
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<tr>
<td>Isradipine</td>
<td>Nil</td>
<td>Hypotension, fatigue, bradycardia and apnoea</td>
<td>Manufacturer suggests avoid</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td></td>
<td></td>
<td>Manufacturer suggests avoid</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>0.08-0.75 &lt;br&gt; 0.07%</td>
<td>No reports of use during human lactation</td>
<td>Excretion into human breast milk should be expected</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>13</td>
<td>1.63</td>
<td>Amount too small to be harmful (but manufacturer suggests avoid)</td>
</tr>
<tr>
<td>Verapamil</td>
<td>0.2-0.92 &lt;br&gt; 0.15-0.98% &lt;br&gt; 0.94</td>
<td>1.2%</td>
<td>Hypotension, bradycardia, weakness</td>
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<tr>
<td>Other antihypertensives</td>
<td></td>
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<tr>
<td>Clonidine</td>
<td>1.54 &lt;br&gt; 23</td>
<td>7.5%</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Methyl dopa</td>
<td>0.2-0.52 &lt;br&gt; 0.19-0.34</td>
<td>0.11</td>
<td>Manufacturer suggests avoid</td>
</tr>
<tr>
<td>Hydralazine</td>
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