

Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in New Zealand

A clinical practice guideline

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Executive summary

Ten priorities for implementation

1. Major risk factors for developing pre-eclampsia include history of pre-eclampsia or HELLP (**H**aemolysis, **E**levated **L**iver enzymes, **L**ow **P**latelet count), chronic hypertension, pre-existing diabetes, renal disease, autoimmune diseases, family history and oocyte donation. Health professionals should identify risk factors when a woman books for antenatal services, make appropriate referrals and begin preventative therapies.
2. Women at high risk of developing pre-eclampsia should begin taking low-dose aspirin and calcium before 16 weeks' gestation to reduce their risk of developing pre-eclampsia and adverse events such as preterm birth.
3. Women who develop severe hypertension in pregnancy (diastolic blood pressure ≥ 110 mmHg or systolic blood pressure ≥ 160 mmHg) should be treated with an antihypertensive.
4. Women with pre-eclampsia should be treated as inpatients.
5. Administering magnesium sulphate is clinically indicated in women with eclampsia. Health professionals should also consider giving magnesium sulphate to women with severe pre-eclampsia; however, the main priority is blood pressure control.
6. When health professionals are considering timing of birth, they need to take into account the severity of the hypertensive disease, gestational age, and the wellbeing of the mother and fetus.
7. The preferred mode of birth is vaginal, unless other maternal or fetal factors contraindicate it.
8. Spinal anaesthesia or combined spinal and epidural anaesthesia (CSE) is the preferred technique for caesarean section, if this is required.
9. Health professionals should monitor women with hypertension in pregnancy for the development or exacerbation of pre-eclampsia postpartum because their blood pressure frequently rises about three to five days after giving birth.
10. Where women have developed gestational hypertension or pre-eclampsia, health professionals should regularly assess them for cardiovascular and renal risk in the long term. A comprehensive discharge letter to the general practitioner should include recommendations for long-term monitoring.

Five research recommendations

1. The National Institute for Health and Care Excellence (NICE) in the United Kingdom recently recommended using the Elecsys immunoassay s-Flt-1/PlGF to 'rule out' development of pre-eclampsia for up to four weeks after the test. However, at the time of publication, (2018) the evidence on the balance of costs and benefits of using these tests in a New Zealand setting is yet to be assessed. Further research using models for predicting pre-eclampsia, which combine different biochemical markers and uterine artery Doppler, is required.
2. Further evidence is needed before health professionals use algorithms that assess the impact of multiple risk factors to predict when pre-eclampsia will occur.
3. Further evidence is needed to determine the optimal monitoring for women with hypertensive disorders in pregnancy. This includes determining which frequency and settings for monitoring provide the best balance between costs and benefits, as well as providers' and women's preferences for different approaches.
4. The current evidence for effectiveness and/or harm of beginning aspirin prophylaxis in the first trimester (before 12 weeks) is limited. Further studies are needed to assess the impact of starting aspirin before 12 weeks' gestation.
5. Very few research findings are available on the educational and support needs of women at high risk of pre-eclampsia or of those experiencing hypertensive disorders in pregnancy.

Scope and purpose of the guideline

Purpose

The purpose of this guideline is to provide an evidence-based summary of best practice in screening, diagnosing and treating hypertension and pre-eclampsia in pregnancy. This includes identifying women at risk, followed by early detection, treatment and follow-up of hypertensive disorders in pregnancy, to promote best clinical practice for these women and their infants.

The guideline is designed for health professionals to use to support their clinical judgement, knowledge and expertise and provide a consistent approach to management and treatment. Health professionals should use it with reference to the individual needs of each woman.

Definitions and classifications

In this guideline, **hypertensive disorders in pregnancy (HDP)** are classified in line with the 2014 revised International Society for the Study of Hypertension in Pregnancy (ISSHP)¹ statement. HDP include:


- chronic/pre-existing hypertension
- gestational hypertension
- pre-eclampsia – de novo or superimposed on chronic hypertension
- eclampsia
- HELLP syndrome (see below for the definition of each of these conditions).

Hypertension: Systolic blood pressure (sBP) is greater than or equal to 140 mmHg **or** diastolic blood pressure (dBP) is greater than or equal to 90 mmHg, as measured on two or more consecutive occasions at least four hours apart.

Chronic/pre-existing hypertension: Hypertension is confirmed before conception or before 20 weeks of gestation with or without a known cause, as measured on two or more consecutive occasions at least four hours apart.


Gestational hypertension: New onset hypertension occurs after 20 weeks' gestation (in a woman who had normal blood pressure before 20 weeks' gestation) and:


- diastolic blood pressure is ≥ 90 mmHg **or** systolic blood pressure is ≥ 140 mmHg
- the woman has none of the abnormalities that define pre-eclampsia
- her blood pressure returns to normal within three months after giving birth.

 It is important to note a rise in baseline blood pressure of 30 mmHg systolic or 15 mmHg diastolic. However, although it may be of clinical importance, it is no longer used to diagnose hypertension.

Pre-eclampsia: The new onset of hypertension occurs after 20 weeks' gestation (in a woman who had normal blood pressure before 20 weeks' gestation) or superimposed on pre-existing hypertension **and one or more** of the following also develop as new conditions:

1. proteinuria – spot urine protein:creatinine ratio ≥ 30 mg/mmol or $\geq 2+$ on dipstick testing confirmed by a protein:creatinine ratio test
2. other maternal organ dysfunction:
 - renal insufficiency (creatinine >90 $\mu\text{mol/L}$, urine output of <80 mL/4 hour)
 - liver involvement - elevated transaminases (aspartate transaminase (AST) and alanine transaminase (ALT)) – at least twice upper limit of normal \pm right upper quadrant or epigastric abdominal pain). Note normal ranges are ALT 0-30 u/L and AST 10-50 u/L
 - neurological complications (common examples are hyperreflexia when accompanied by clonus, severe headaches and persistent visual scotomata; other examples are eclampsia, altered mental status, blindness, stroke)
 - haematological complications (thrombocytopenia – platelet count below $100 \times 10^9/\text{L}$, haemolysis)
3. uteroplacental dysfunction (eg, fetal growth restriction, abruption). Each of the following is a **severe feature of pre-eclampsia**:
 - **severe hypertension** (DBP ≥ 110 mmHg **or** sBP ≥ 160 mmHg)
 - **thrombocytopenia** (platelet count less than $100 \times 10^9/\text{L}$)
 - **impaired liver function** not responding to treatment and not accounted for by alternative diagnosis – elevated transaminases (AST and ALT) – at least twice the upper limit of normal \pm right upper quadrant or epigastric abdominal pain (may be referred to upper back)
 - progressive renal insufficiency (serum creatinine >90 $\mu\text{mol/L}$ or doubling of serum creatinine concentration in the absence of other renal disease, urine output of <80 mL/4 hour)
 - pulmonary oedema
 - new onset of headaches and visual disturbances
 - HELLP syndrome
 - eclampsia.

 Proteinuria is not essential for a pre-eclampsia diagnosis.

 Eclamptic seizures are self-limiting, have no persistent clinical neurological features and are not caused by pre-existing neurological conditions.

Unstable pre-eclampsia: Women with pre-eclampsia have worsening pre-eclampsia blood results and severe hypertension not controlled by antihypertensives. Also known as fulminating pre-eclampsia.

Eclampsia: New onset of seizures occurs in association with pre-eclampsia. It is a severe manifestation of pre-eclampsia and can occur before, during or after birth. It can be the presenting feature of pre-eclampsia in some women.

HELLP syndrome: A variant of severe pre-eclampsia (elements include **H**aemolysis, **E**levated **L**iver enzymes and **L**ow **P**latelet count). In a woman with pre-eclampsia, the presence of any of the following is an indicator of HELLP:

- maternal platelet count of less than $100 \times 10^9/\text{L}$
- elevated transaminases (elevated blood concentrations of liver enzymes to twice the normal concentration)
- microangiopathic haemolytic anaemia with red cell fragments on blood film.

The need for the guideline

The New Zealand Ministry of Health identified a need for:

- an evidence-based guideline developed in consultation with the wider New Zealand maternity sector for diagnosing and treating hypertension and pre-eclampsia in pregnancy
- a plan to inform and monitor implementation of that guideline.

In 2009 the Government launched the Maternity Quality Initiative, which included the establishment of a Maternity Quality and Safety Programme. During the planning for the Programme, and in response to recommendations from the Perinatal and Maternal Mortality Review Committee and the Minister of Health, it was agreed that a nationally endorsed clinical guideline be developed to help achieve more consistent service provision.

Pre-eclampsia complicates approximately 3–8% of pregnancies in New Zealand,² and hypertensive disorders together affect about 5–10% of pregnancies (4–5% nulliparous; 2–3% in low-risk multiparas and up to 20% in women with major risk factors).³ Chronic hypertension, gestational hypertension and pre-eclampsia have increased over time as a result of changes in the characteristics of mothers (such as in their age and pre-pregnancy weight), whereas eclampsia has declined following on from widespread antenatal care and use of prophylactic treatments (such as magnesium sulphate).^{4,5}

A World Health Organization (WHO) review identified hypertension as the single leading cause of maternal mortality in developed countries, accounting for 16% of maternal deaths.⁶ Perinatal mortality is also high for women who experience pre-eclampsia.⁷ Hypertensive disorders in pregnancy are linked with acute and long-term morbidity in mothers and babies.^{8,9,10,11}

Practices in diagnosing and treating women with hypertensive disorders in pregnancy vary throughout New Zealand, with several guidelines and local protocols available. The proportion of women admitted to hospital with eclampsia, which is an indicator of severe maternal morbidity, also varies across district health boards.⁹ These differences highlight the need for a consistent approach using evidence-based guidance on how to diagnose and treat hypertensive disorders in pregnancy in New Zealand.

Scope of the guideline

This guideline covers recommendations for:

- identifying women in New Zealand at high risk of developing hypertensive disorders in pregnancy
- diagnosing and treating women with these conditions
- following up women with hypertensive disorders in pregnancy after birth.

Target audience

This guideline is intended for the providers of maternity care. It also has implications for health service provider organisations, funders of maternity services and funders in primary and secondary care. Women with hypertensive disorders in pregnancy and their families and whānau may use it as well.

The Guideline Development Team (GDT) has been committed to including consumers as it has developed the guideline. Consumers are an integral part of the team and have helped to evaluate the evidence and develop the recommendations.

Treaty of Waitangi

The GDT acknowledges the importance of the Treaty of Waitangi to New Zealand. It believes the Treaty principles of partnership, participation and protection are central to improving Māori health.

The GDT has specifically considered Māori health issues that are relevant to the guideline and its implementation. It has looked at particular barriers in the guideline development process where Māori health must be considered and addressed. At all other points in the guideline, it has taken account of Māori health in a less explicit manner.

Guideline development process

The GDT followed a structured process for guideline development. (See Appendix A for a more detailed description of this process.)

In summary, key stakeholder groups, who the Ministry of Health and the research group had identified, nominated the members of the multidisciplinary GDT (see Appendix B for a list of the members). The GDT held two face-to-face meetings, each lasting one day. Here the research team presented evidence along with eight clinical questions that guided systematic and narrative reviews of the evidence. The different levels of evidence interrogated included (but were not limited to) existing clinical practice guidelines, systematic reviews, randomised controlled trials and observational studies. To give the guideline greater continuity, the GDT has included New Zealand-specific evidence or data (where available) in each evidence statement. The GDT reviewed all evidence and developed recommendations. It also reviewed and commented on all drafts and approved the final version of the guideline. (See Appendix C for the conflict of interest disclosures from the GDT.)

For the clinical questions and a list of high-priority maternal and fetal outcomes, see Appendices D and E.

The Guideline Development Team adapted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method, which allowed it to grade its clinical practice recommendations based on the strength and quality of the evidence, together with values and preferences in the New Zealand health care setting. It made recommendations both for and against clinical practice. Where insufficient evidence is available to make a recommendation, or in areas where a narrative review has been conducted, the GDT has made a practice point (✓ ✗) based on expert opinion or consensus. Where high-quality evidence is not available to make a recommendation, the GDT has made a research recommendation. For a summary of the GRADE approach, see Appendix F.

Implementation plan and resource implications

Implementation plan

The GDT has developed a recommended implementation plan alongside this guideline and provided it to the guideline funder (the Ministry of Health).

Resource implications

The GDT has made recommendations based on the best evidence available without taking account of restrictions related to cost or resources. We have, however, identified the following major resource implications.

- The recommendations around increased monitoring for women at high risk of or diagnosed with a hypertensive disorder in pregnancy may place additional demands on lead maternity carers, particularly in rural areas. District health boards may need to consider additional resourcing to reduce these demands.
- The recommended increase in postnatal and long-term monitoring of women who have experienced a hypertensive disorder in pregnancy will increase costs for these women through additional visits to their general practitioner (GP). On the other hand, they should gain better health outcomes.

- Psychological care and support for women, as recommended, may increase demands on mental health services so district health boards may need to consider additional resourcing in this area. However, women showing signs of psychological distress or depression are likely to significantly increase health care costs in the long term if they are untreated.

In addition, it is likely that all of the above costs will be offset by a decrease in the long-term costs involved in addressing neonatal and maternal adverse events, if the number of these events falls as expected.

Funding of the guideline

The Ministry of Health has commissioned and funded this guideline. A representative of the Ministry of Health attended each Guideline Development Team meeting in an ex officio capacity and had no influence on the development of the clinical recommendations.

Endorsements

The following professional colleges have endorsed the guidelines

- The Royal Australian and New Zealand College of Obstetricians and Gynaecologists
- The Australian and New Zealand College of Anaesthetists
- The Royal New Zealand College of General Practitioners
- The New Zealand College of Midwives

Recommendations

This section sets out the evidence-based recommendations and practice points the Guideline Development Team has developed. The structure follows the course of pregnancy with four groups of recommendations: pre-conception, antenatal, intrapartum and postpartum considerations.

Alongside each recommendation is a grade for the quality of the evidence that has informed the recommendation. Also noted is the strength of the recommendation.

The grade for the **quality of evidence** for each outcome is based on five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias). The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on how the GDT has assessed it for being at risk of bias, indirect, seriously inconsistent, imprecise in its effect estimates or involved in potential publication bias.

The **strength of recommendation** reflects the extent to which the GDT is confident that the benefits of a recommended intervention outweigh its harms, or vice versa. The strength of recommendation is influenced by the quality of supporting evidence, the balance between desirable and undesirable effects, and the perceived variability or uncertainty in a woman's values and preferences related to the intervention.

This GRADE approach is used or endorsed by 100 organisations from 19 countries, including the National Institute for Health and Care Excellence (NICE), Cochrane, UpToDate and the *British Medical Journal* (BMJ).

The practice points appear in boxes throughout this section. This guideline strongly encourages practices marked whereas it strongly discourages those marked .

1. Pre-conception counselling

- Where any woman has a history of pre-eclampsia or hypertension in pregnancy or chronic hypertension, offer her pre-conception counselling and a referral to an obstetric service. Women who want to become pregnant and are on antihypertensive drugs should discuss, with their specialist, changing from an angiotension converting enzyme (ACE) inhibitor to an alternative medication, if applicable.

Strong recommendation; low-quality evidence

2. Antenatal

- As early as possible in pregnancy or when the woman books for antenatal services, make risks for pre-eclampsia and hypertensive disorders part of a full health assessment (see 'Risk factors for pre-eclampsia'). Refer women with existing hypertension for consultation with an obstetric specialist. See lifestyle, calcium and aspirin sections for guidance on these issues.

Risk factors for pre-eclampsia

- As part of a comprehensive health assessment at booking, review all women for the risk factors for pre-eclampsia (Table 1). This will help to appropriately identify the most at-risk women. Women who have a major risk factor (MRF) have an approximately 20% risk of developing pre-eclampsia and should be considered as high risk.¹²

Strong recommendation; low-quality evidence

- Models are currently insufficient to determine a cumulative increase in risk of pre-eclampsia if a woman has multiple risk factors. However, give special consideration to a woman with several risk factors.

Weak recommendation; high-quality evidence

Table 1: Increased risk of developing pre-eclampsia if woman has pre-existing risk factors

Pre-existing risk factor	Relative risk/ odds ratio	95% CI	Notes
Antiphospholipid antibodies/SLE	9.72 ^b	4.34–21.75	MRF
Previous history of pre-eclampsia	7.19 ^b	5.85–8.83	MRF
ART (oocyte donation) ¹³	4.34 ^a	3.10–6.06	MRF
Renal disease ¹⁴	4.07 ^a	2.17–7.66	MRF
Chronic hypertension	3.6 ^a	2.0–6.6	MRF
Previous history of HELLP ¹⁵	3.7 ^a	0.9–16.1	MRF
Pre-existing diabetes	3.56 ^b	2.54–4.99	MRF
Family history of pre-eclampsia in mother or sister	3.3	1.5–7.4	MRF
Genetic ancestry			
– African ¹⁶	2.97 ^a	1.98–4.4	
– Indian	2.66 ^a	1.29–5.48	
– Māori ¹⁷	1.51 ^a	1.16–1.96	
– Pacific	1.21 ^a	0.99–1.57	
Nulliparity	2.91 ^b	1.28–6.61	
Multiple pregnancy	2.93 ^b	2.04–4.21	
Family history of pre-eclampsia	2.9 ^a	1.70–4.93	
Father of baby ¹⁸	2.1	1.0–4.3	
Change in partner ¹⁹	2.5 ^b	1.8–3.5	
Elevated BMI ≥35 (early/pre-pregnancy)	2.47 ^a	1.78–3.15	
Maternal age ≥40 (multiparous)	1.96 ^b	1.34–2.87	
Maternal age ≥40 (primiparous)	1.68 ^b	1.23–2.29	
Pregnancy interval >10 years	1.83 ^b	1.72–1.94	
ART (sperm donation) ²⁰	1.63 ^a	1.36–1.95	
Diastolic BP ≥80 mmHg at booking	1.38 ^b	1.01–1.87	
Any ART ²¹	1.17 ^a	1.10–1.24	

Adjusted odds ratio b. Relative risk. Data from Duckitt and Harrington (2005)²² unless otherwise referenced

ART = assisted reproductive technology; BMI = body mass index; BP = blood pressure; CI = confidence interval;

HELLP = Haemolysis, Elevated Liver enzymes and Low Platelet count; MRF= major risk factor; SLE = systemic lupus erythematosus.

Predictive testing

- Models for predicting pre-eclampsia, which combine different biochemical markers and uterine artery Doppler for all women, have shown mixed results. This guideline does not currently recommend using them. Although some show promise as potential screening tools, the evidence and experience of using them in clinical settings are not conclusive enough to include in this guideline.

Weak recommendation; very low-quality evidence

Women's experience

- Make educational tools available to help women understand issues relating to hypertension in pregnancy and pre-eclampsia. Such tools should take into consideration women's different levels of health literacy and demographic diversity.

Strong recommendation; very low-quality evidence

- Work is needed to ensure equity of care for all women, in particular, Māori and Pacific women who are over-represented in poor obstetric outcomes.

Strong recommendation; very low-quality evidence

- It is a priority to give women the opportunity to discuss their options for management of care with practitioners with clinical experience and knowledge of current research about hypertensive disorders in pregnancy.

Strong recommendation; very low-quality evidence

- Complications associated with hypertensive disorders in pregnancy can be very stressful. Assess, address and document women's need for psychological care and support (eg, community organisations, mental health services and cultural support), both antenatally and postpartum.

Strong recommendation; very low-quality evidence

- Actively involve women and their families and whānau and keep them informed throughout the health decision-making process.

Strong recommendation; very low-quality evidence

☑ Assess and address barriers to effective communication with vulnerable groups of women, such as literacy, language, geographical, socioeconomic and cultural barriers.

☑ Offer a referral to support agencies, such as social work support, to all women with pre-eclampsia.

Lifestyle

- Excessive weight gain in pregnancy puts women at risk of developing hypertensive disorders. This risk is even greater in women who are obese when they become pregnant. An optimal gestational weight gain for these women is 5–9 kg. Give specific education around optimal weight gain.

Weak recommendation; very low-quality evidence

- Give routine advice on healthy eating, smoking cessation, alcohol intake and mild to moderate exercise to all women in the antenatal period, as well as weighing them regularly. Further randomised control trials are needed to determine the effects of these interventions on hypertensive disorders in pregnancy.

Strong recommendation; low-quality evidence

- Folic acid and iodine supplements are recommended in all pregnancies to reduce the risk of spina bifida and promote normal brain development. However, no conclusive evidence is available to indicate that these supplements reduce the risk of developing HDP or pre-eclampsia.

Weak recommendation; low-quality evidence

☑ Controlling blood pressure level is vital at any stage of care. This will not prevent pre-eclampsia but will reduce the risk of stroke and poor outcomes for the mother.

- Currently there is no strong evidence to show that multi-vitamins or other supplements such as fish oil and magnesium reduce the risk of developing HDP or pre-eclampsia.
Strong recommendation; moderate-quality evidence
- This guideline does not recommend vitamin C and vitamin E supplementation. Such supplementation may cause harm because high levels (eg, vitamin C 1,000 mg and vitamin E 400 IU) are linked with an increased risk of low birthweight babies.
Strong recommendation; moderate-quality evidence
- This guideline does not recommend salt restriction in women at risk of pre-eclampsia.
Strong recommendation; moderate-quality evidence
- This guideline does not recommend bed rest and restriction of physical activity in women at risk of pre-eclampsia.
Strong recommendation; very low-quality evidence

Aspirin

- Aspirin (100 mg daily) is indicated in women at high risk of developing pre-eclampsia. They should begin taking it before 16 weeks' gestation. Evidence on the efficacy and safety of starting low-dose aspirin before 12 weeks' gestation is currently limited.
Strong recommendation; moderate-quality evidence
- Women can remain on aspirin until they give birth.
Weak recommendation; very low-quality evidence

Effectiveness of aspirin is improved in pregnancy if taken at night.

The numbers needed to treat, to prevent one case of pre-eclampsia, using aspirin and calcium are listed in Table 2.

Table 2: Numbers needed to treat (NNT) to prevent one case of pre-eclampsia

Treatment	Women at high risk of pre-eclampsia
Aspirin	56
Calcium	7

Calcium

- For women at high risk of pre-eclampsia, offer calcium supplementation along with dietary advice to achieve 1 g elemental intake per day, from booking to birth.
Strong recommendation; moderate-quality evidence

Antihypertensives

- Urgently treat all women with severe hypertension (dBP \geq 110 or sBP \geq 160 mmHg) with antihypertensives to acutely lower blood pressure.
Strong recommendation; low-quality evidence
- Consider antihypertensives for women with gestational hypertension (dBP \geq 90 or sBP \geq 140 mmHg), especially those with risk factors and/or co-morbidities.
Strong recommendation; very low-quality evidence
- As well as taking account of the evidence and clinical experience, consider the choice of antihypertensive drug in the context of resource availability, the local health care setting and the condition of the individual woman.
Strong recommendation; very low-quality evidence

- Emphasise educating women so that they clearly understand the importance of taking their antihypertensive drugs as prescribed, the symptoms of HDP and when to report symptoms.
Weak recommendation; very low-quality evidence
- First-line antihypertensives to use in treating HDP include: labetalol, nifedipine and methyldopa
Strong recommendation; very low-quality evidence

Acute lowering of severe hypertension

The antihypertensive regimen for acute lowering of blood pressure in women with severe hypertension (dBP \geq 110 or sBP \geq 160 mmHg) differs from the regimen for chronic management.

See Box 1 below for acute treatment options.

- ☑ Target blood pressure levels are:
 - dBP from 80–100 mmHg
 - sBP from 130–150 mmHg.

Box 1: Antihypertensive agents for acute lowering of severe hypertension

Start one of these regimens in all women with severe hypertension (dBP \geq 110 or sBP \geq 160 mmHg).

Nifedipine

10 mg conventional release tablet (oral)
Onset of action: 30–45 minutes
Onset of maximum effect: 30 minutes
Repeat: after 30–45 minutes (if needed)
Maximum: 80 mg daily

Labetalol

Initially 20 mg IV bolus over 2 minutes
Onset of action: 5 minutes
Onset of maximum effect: 10–15 minutes
Repeat with 40–80 mg
Repeat: every 10 minutes (if needed)
Maximum: 300 mg

Hydralazine

5–10 mg IV bolus over 3–10 minutes (5 mg if fetal compromise)
Onset of action: 20 minutes
Onset of maximum effect: 10–80 mins
Repeat: every 20 minutes
Maximum: 30 mg
Consider IV bolus of crystalloid fluid before or when administering the first IV hydralazine dose (usually 200–300 mL)


Antenatal monitoring


- Educate women (and their families and whānau) fully around the need to contact their lead maternity carer (LMC) urgently if they experience symptoms of pre-eclampsia.
Strong recommendation; very low-quality evidence

- ☑ Where possible women with a major risk factor for pre-eclampsia should have uterine artery Doppler studies performed at their 20-week anatomy scan. The result of this assessment can be used to plan the schedule for serial growth assessment.

These symptoms include:

- severe headache
- problems with vision, such as blurring or flashing before the eyes
- severe epigastric pain or right upper quadrant pain
- vomiting
- sudden swelling of the face, hands or feet.

 Evidence shows elevations in serum uric acid (hyperuricemia) are a poor predictor of pre-eclampsia and so this is not essential to test.

 Testing 24-hour urinary protein is not usually necessary, as evidence shows it is no more predictive than a spot protein:creatinine ratio (PCR) test.

- A woman presenting with features of pre-eclampsia requires urgent (same day) referral to an obstetric specialist and a transfer of care (referral code 4022). Usually the woman will be admitted to hospital.


Strong recommendation; very low-quality evidence

- For women managed as outpatients, base the frequency of additional antenatal appointments (from the conventional appointment schedule) on each woman's individual needs, the severity of her condition and her preferences.

Strong recommendation; very low-quality evidence

- Refer women with hypertension in pregnancy for a full assessment by an obstetric specialist (referral code 4009). The specialist should make a plan of who is going to carry out the ongoing care and monitoring of the woman and her baby in conjunction with the woman, the LMC and GP.

Strong recommendation; very low-quality evidence

 Make a clear management plan for all women with hypertensive disorders in pregnancy. The plan should include clinical responsibilities and reflect the woman's preferences.


 Consider the practical (social and economic) implications of inpatient care from the woman's perspective.

Table 3 summarises monitoring needs of women with hypertensive disorders in pregnancy.

Table 3. Monitoring requirements for women with hypertensive disorders in pregnancy

Pre-existing/ chronic	Gestational hypertension	Pre-eclampsia /expectant management (hospital inpatient)	Severe unstable pre-eclampsia/ eclampsia (hospital inpatient)	Magnesium sulphate monitoring (high dependency-like setting)	Intrapartum pre-eclampsia/ eclampsia	Postpartum
Identify risk factors	Blood pressure 1–2 times a week	4–6 hourly blood pressure (except overnight when an interval of 8 hours is acceptable)	One-on-one care	One-on-one care	Blood pressure at least hourly	Recommend women who have had pre-eclampsia stay in secondary or tertiary facility for at least 72 hours postpartum
			Hourly blood pressure , respiratory rate, oxygen saturation	Blood pressure every 5 minutes during loading dose then hourly during maintenance dose		
Consider more frequent blood pressure measurements and appointments than normal if for pregnant women who have any of the risk factors and unstable pre-eclampsia; individualise decision to the woman	Proteinuria at least weekly ^a	Twice weekly pre-eclampsia bloods = full blood count (including haemoglobin, platelet count), creatinine, electrolytes, liver function tests (albumin, ALT and AST)	At least daily pre-eclampsia bloods = full blood count (including haemoglobin, platelet count), creatinine, electrolytes, liver function tests (albumin, ALT and AST)	At least daily pre-eclampsia bloods = full blood count (including haemoglobin, platelet count), creatinine, electrolytes, liver function tests (albumin, ALT and AST)	Urine output or fluid balance	Base the decision for discharge timing on the individual woman and on whether satisfactory monitoring and follow-up care arrangements have been made
	Pre-eclampsia bloods if sudden increase in BP or new proteinuria				Continuous cardiotocography	
	Fetal assessment at time of diagnosis. Do not repeat USS in <2 weeks, unless fetal indications ^b				Perform coagulation studies if liver tests are abnormal or you have concerns about possible placental abruption	Perform coagulation studies if liver tests are abnormal or you have concerns about possible placental abruption

Pre-existing/ chronic	Gestational hypertension	Pre-eclampsia /expectant management (hospital inpatient)	Severe unstable pre-eclampsia/ eclampsia (hospital inpatient)	Magnesium sulphate monitoring (high dependency-like setting)	Intrapartum pre-eclampsia/ eclampsia	Postpartum
Ongoing fetal assessment ^b for growth. If IUGR detected, follow the SGA pathway	Changes in fetal movements , other signs/ symptoms of pre-eclampsia. The woman assesses daily and her maternity carers when they see her	Repeat laboratory investigations more often if you have concerns about the condition of either mother or fetus	Repeat laboratory investigations more often if you have concerns about the condition of either mother or fetus	Repeat laboratory investigations more often if you have concerns about the condition of either mother or fetus		After discharge, blood pressure daily for first 7 days, then weekly up to 6 weeks postpartum
		Cardiotocography (CTG) daily if inpatient	Cardiotocography daily	Continuous cardiotocography		
		Symptoms of labour (presence of contractions, rupture of membranes, abdominal pain, bleeding)	Fluid restriction 80–85 mL/hour total fluid for severe pre-eclampsia	Toxicity monitoring		
				Respiratory rate/SpO₂ hourly		
Symptoms of severe pre-eclampsia (headaches, visual changes, shortness of breath, epigastric pain, retrosternal pressure/pain, nausea, vomiting, hyperreflexia)	Fluid balance chart	Patella reflexes hourly				
		Urine output (>100 mL over 4 hours)				
		Symptoms of labour (presence of contractions, rupture of membranes, abdominal pain, bleeding)				

a. Urinalysis by dipstick followed by spot urine PCR if $\geq 2+$ proteinuria. Once significant proteinuria has been detected, there is no established role for serial testing. b. Fetal assessment with ultrasound for early dating and fetal growth at the time of diagnosis, and repeat if suspected growth restriction on clinical assessment by LMC. Umbilical artery velocimetry and cardiotocography only if fetal growth restriction or distress is suspected. c. Educate the woman around the need to contact her LMC urgently if she experiences symptoms of pre-eclampsia/eclampsia or any changes in fetal movements. ALT = alanine aminotransferase, AST = aspartate aminotransferase, BP=blood pressure, IUGR = intrauterine growth restriction, SGA = small for gestational age, SpO₂ = peripheral capillary oxygen saturation, USS = ultrasound scan

Treatment summaries

Pre-existing/chronic hypertension

(Hypertension confirmed pre-conception or before 20 weeks gestation)

Pre-pregnancy or at first visit

- Change from ACE inhibitors to alternative antihypertensive
- Note increased risk factor for pre-eclampsia
- Initiate calcium
- Initiate aspirin from 12 weeks' gestation
- Refer to obstetric team (see referral codes 1014, 1015)
- Educate about signs and symptoms of pre-eclampsia

First-line antihypertensives

- Labetalol
- Nifedipine
- Methyldopa

Maternal monitoring

- Begin usual schedule of antenatal visits but monitor blood pressure more closely if blood pressure is unstable
- Aim to control hypertension at pre-pregnancy range or lower

Fetal monitoring

If scanning raises fetal growth concerns:

- conduct USS, AFV, umbilical artery Doppler and CTG if indicated
- follow SGA guidelines for management if diagnosed

Timing of birth

- **Before 37 weeks:** Do not recommend birth unless other maternal or fetal indications support it
- **After 37 weeks:** For women with low risk of adverse outcomes, consider expectant management beyond 37 weeks with increased monitoring

Intrapartum

- At least hourly BP in labour
- Continue antihypertensives

Postpartum

- If on methyldopa, consider changing to another antihypertensive, eg, ACE inhibitor
- Daily BP to 7 days after birth, then at least weekly to 6 weeks
- Give woman's GP a comprehensive discharge summary

ACE = angiotensin converting enzyme; AFV = amniotic fluid volume; BP = blood pressure; CTG = cardiotocograph; GP = general practitioner; SGA = small for gestational age; USS = ultrasound scan

Gestational hypertension

New onset of hypertension after 20 weeks' gestation without signs of pre-eclampsia and dBP ≥ 90 OR sBP ≥ 140 mmHg

At diagnosis

- Spot urine protein creatinine ratio (PCR)
- Pre-eclampsia bloods
- Prompt referral to obstetric team (see referral code 4009)
- Assess fetal growth/wellbeing (USS, umbilical artery Doppler assessment and CTG if indicated)
- Consider initiating first-line antihypertensives
- Educate about signs and symptoms of pre-eclampsia

Maternal monitoring

- The obstetric team makes a management plan for ongoing care and monitoring in discussion with the woman and her LMC
- Carry out BP and urinalysis for protein at least weekly
- If sudden increase in BP or new proteinuria, or other signs of pre-eclampsia, do pre-eclampsia bloods and PCR

Fetal monitoring

If scanning raises fetal growth concerns:

- conduct USS, AFV, umbilical artery Doppler and CTG if indicated
- follow SGA guidelines for management if diagnosed

Timing of birth

- **Before 37 weeks:** Recommend expectant management. Do not recommend birth unless other maternal or fetal indications support it
- **After 37 and before 40 weeks:** Consider birth. The woman, her LMC and the obstetric team should negotiate the timing together

Intrapartum

- At least hourly BP in labour
- Continue antihypertensives – adjust if necessary for other factors, eg, neuraxial anaesthesia

Postpartum

- If on methyldopa, consider changing to another antihypertensive, eg, ACE inhibitor
- Daily BP to 7 days after birth, then at least weekly to 6 weeks
- Give woman's GP a comprehensive discharge summary

First-line

Antihypertensives

- Labetalol
- Nifedipine
- Methyldopa

Pre-eclampsia bloods

- FBC
- Electrolytes
- Creatinine
- LFT (incl AST, ALT)
- Coagulation if AST ALT abnormal/low platelets

Signs and symptoms of pre-eclampsia

- Severe headache
- Visual disturbances
- Severe epigastric pain
- Shortness of breath
- Retrosternal pressure/pain
- Nausea, vomiting
- Sudden swelling of face, hands or feet
- Hyperreflexia

Antihypertensives and breastfeeding

- Establish breastfeeding if desired
- Change to compatible antihypertensive, eg, ACE inhibitor
- Very pre-term babies may have an increased risk of adverse effects from antihypertensives

ACE = angiotensin converting enzyme; AFV = amniotic fluid volume; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; CTG = cardiotocograph; dBP = diastolic blood pressure; FBC = full blood count; GP = general practitioner; LFT = liver function test; sBP = systolic blood pressure; SGA = small for gestational age; USS = ultrasound scan

Pre-eclampsia

Hypertension (dBP \geq 90 mmHg OR sBP \geq 140 mmHg) + other signs and symptoms
(refer to definitions)

At diagnosis

- Immediately consult with obstetric team. Transfer of care recommended (referral code 4022)
- Blood pressure control of primary importance. Start first-line antihypertensive if dBP \geq 90 mmHg OR sBP \geq 140 mmHg or acute regimen if dBP \geq 110 mmHg OR sBP \geq 160 mmHg. Aim for target BP 140/100 mmHg or lower
- Admit to secondary or tertiary facility
- Spot urine protein: creatinine ratio (PCR)
- Pre-eclampsia bloods
- Assess fetal growth/wellbeing (USS, umbilical artery Doppler assessment and CTG if indicated)
- Educate about signs and symptoms of worsening pre-eclampsia

Maternal monitoring

- The obstetric team makes a management plan for ongoing care and monitoring in discussion with the woman and her LMC
- BP 4–6 hourly (except overnight when an interval of 8 hours is acceptable)
- Clinical deterioration can be rapid
- Twice weekly pre-eclampsia bloods
- Conduct coagulation studies if liver function tests are abnormal or you have concerns about possible placental abruption

Fetal monitoring

- Follow SGA guidelines for management if diagnosed
- After assessment at the time of diagnosis, do not repeat USS for growth in <2 weeks
- Daily CTG if inpatient

Timing of birth

- **Before 37 weeks: (eg, 36+6):** Adopt expectant approach. Do not recommend delivery in the absence of other maternal indicators (eg, premature rupture of membranes, preterm labour or vaginal bleeding, deterioration of condition) or fetal indications. Should usually be managed as an inpatient.
- **After 37 weeks: (eg, 37+0):** Recommend birth. No appreciable benefit in continuing pregnancy after 37 weeks. The woman, her LMC and the obstetric team should negotiate the timing and method.

Intrapartum

- At least hourly BP in labour
- Continue antihypertensives – adjust if necessary for other factors, eg, neuraxial anaesthesia
- Fluid balance monitoring

Postpartum

- If on methyldopa, consider changing to another antihypertensive, eg, ACE inhibitor
- Continue to monitor for disease resolution, titrate antihypertensives as required
- Advise to stay in secondary/tertiary facility for at least 72 hours (4–6 hourly BP)
- Daily BP to 7 days after birth, then at least weekly to 6 weeks
- Give woman's GP a comprehensive discharge summary
- 6-week obstetric review

First-line antihypertensives

- Labetalol
- Nifedipine
- Methyldopa

Antihypertensives for acute lowering of BP

if dBP \geq 110 mmHg OR sBP \geq 160 mmHg

Nifedipine

10 mg conventional release tablet (oral)

Onset: 30–45 minutes

Repeat: after 30–45 minutes (if needed)

Maximum: 80 mg daily

Labetalol

Initially 20 mg IV bolus over 2 minutes

Onset: 5 minutes

Repeat with 40–80 mg

Repeat: every 10 minutes (if needed)

Maximum: 300 mg

Hydralazine

5–10 mg (5 mg if fetal compromise

IV bolus over 3–10 minutes)

Onset: 20 minutes

Repeat: every 20 minutes (if needed)

Maximum: 30 mg (consider IV bolus ocrystalloid fluid before or when administering first IV hydralazine dose (usually 200–300 mL)

Pre-eclampsia bloods

- FBC
- Electrolytes
- Creatinine
- LFT (incl AST, ALT)
- Coagulation if AST, ALT abnormal/low platelets

Signs and symptoms of pre-eclampsia

- Severe headache
- Visual disturbances
- Severe epigastric pain
- Shortness of breath
- Retrosternal pressure/pain
- Nausea, vomiting
- Sudden swelling of face, hands or feet
- Hyperreflexia

ACE = angiotensin converting enzyme; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; CTG = cardiotocograph; dBP = diastolic blood pressure; FBC = full blood count; GP = general practitioner; IV = intravenous; LFT = liver function test; LMC = lead maternity carer; sBP = systolic blood pressure; SGA = small for gestational age; USS = ultrasound scan

Severe/unstable pre-eclampsia

Uncontrolled severe hypertension (dBp \geq 110 mmHg OR sBP \geq 160 mmHg) + worsening PE bloods + other signs and symptoms (refer to definitions)

At diagnosis

- Consult immediately with obstetric team. Transfer of care recommended (referral code 4022)
- BP control of primary importance. Initiate acute antihypertensive care regimen, aim for target BP 140/100 mmHg or lower
- Also consider magnesium sulphate to prevent a primary seizure
- Admit to secondary or tertiary facility
- Spot urine protein: creatinine ratio (PCR)
- Pre-eclampsia bloods
- Assess fetal growth (umbilical artery Doppler assessment and CTG, if indicated)

Maternal monitoring

- Management plan should include discussions with the obstetric and anaesthetic teams along with the woman and the LMC
- Hourly BP and respiratory rate
- Fluid balance chart
- At least daily pre-eclampsia bloods
- Conduct coagulation studies if liver function tests are abnormal or you have concerns about possible placental abruption

Maternal monitoring – magnesium sulphate

- Blood pressure every 5 minutes during bolus dose, then hourly during maintenance dose
- Respiratory rate, O₂ saturation, reflexes hourly
- Urine output (>100 mL over 4 hours)
- Fluid restriction (replace loss at delivery and then 80–85 mL/hour total fluid)

Fetal monitoring

- Follow SGA guidelines for management if diagnosed
- After assessment at time of diagnosis, do not repeat growth USS in <2 weeks
- Daily CTG (continuous if magnesium sulphate running)

Timing of birth

- **Peri-viability and before:** Manage in a tertiary setting with maternal fetal medicine involvement if possible, and with careful discussion with the woman
- **Before 34 weeks:** Adopt expectant approach in a secondary or tertiary centre with resources for maternal and fetal monitoring and critical care of the mother and the baby. If indication for birth presents, administer corticosteroids for fetal lung maturation and magnesium sulphate for fetal neuroprotection (if <30 weeks). Not required if already on magnesium sulphate.
- **After 34 weeks:** Recommend birth after stabilising the woman in a centre with appropriate resources for care of the mother and baby

Intrapartum

- At least hourly BP in labour
- CTG
- Continue antihypertensives – adjust if necessary for other factors, eg, effect of magnesium sulphate, neuraxial anaesthesia

Postpartum

- Continue magnesium sulphate for 24 hours
- If on methyl dopa, consider changing to another antihypertensive, eg, ACE inhibitor
- Continue to monitor for disease resolution, titrate antihypertensives as required
- Advise to stay in secondary/tertiary facility for at least 72 hours (4–6 hourly BP)
- Daily BP to 7 days after birth, then at least weekly to 6 weeks
- Give woman's GP a comprehensive discharge summary
- 6-week obstetric review

Antihypertensives for acute lowering of BP

Nifedipine

10 mg conventional release tablet (oral)

Onset: 30–45 minutes

Repeat: after 30–45 minutes (if needed)

Maximum: 80 mg daily

Labetalol

Initially 20 mg IV bolus over 2 minutes

Onset: 5 minutes

Repeat with 40–80 mg

Repeat: every 10 minutes (if needed)

Maximum: 300 mg

Hydralazine

5–10 mg (5 mg if fetal compromise)

IV bolus over 3–10 minutes

Onset: 20 minutes

Repeat: every 20 minutes (if needed)

Maximum: 30 mg (consider IV bolus of crystalloid fluid before or when administering first IV hydralazine dose, usually 200–300 mL)

Magnesium sulphate

To prevent progression to eclampsia, this anticonvulsant drug may be administered – **see protocol**

Pre-eclampsia bloods

- FBC
- Electrolytes
- Creatinine
- LFT (incl AST, ALT)
- Coagulation if AST, ALT abnormal/low platelets

Signs and symptoms of pre-eclampsia

- Severe headache
- Visual disturbances
- Severe epigastric pain
- Shortness of breath
- Retrosternal pressure/pain
- Nausea, vomiting
- Sudden swelling of face, hands or feet
- Hyperreflexia

ACE = angiotensin converting enzyme; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; CTG = cardiotocograph; dBp = diastolic blood pressure; FBC = full blood count; GP = general practitioner; IV = intravenous; LFT = liver function test; LMC = lead maternity carer; O₂ = oxygen; PE = pulmonary embolism; SGA = small for gestational age; sBP = systolic blood pressure; USS = ultrasound scan

Eclampsia

New onset of seizures in association with pre-eclampsia

At diagnosis

- Immediately consult with obstetric team. Transfer of care (referral code 4006)
- Immediate Airway, Breathing, Circulation, Disability, Exposure (ABCDE) management
- BP control of primary importance if severe
- Admit to secondary/tertiary facility
- Pre-eclampsia bloods + coagulation bloods
- Assess fetal growth (umbilical artery Doppler assessment and cardiotocography if indicated)

Treatment

- Only conclusive treatment is birth of baby but aim to stabilise and monitor if possible if <37 weeks' gestation
- Begin magnesium sulphate – see protocol
- If hypertensive, start antihypertensive, aim for a target BP below 140/100 mmHg

Maternal monitoring

- One-to-one midwifery care
- Management should include discussion with the anaesthetic and intensive care teams but with obstetric lead
- Continuous SpO₂ monitoring
- Fluid balance
- At least daily pre-eclampsia bloods
- Conduct coagulation studies if liver function tests are abnormal or you have concerns about possible placental abruption

Maternal monitoring – magnesium sulphate

- Maternal monitoring – magnesium sulphate
- Blood pressure every 5 minutes during bolus dose then hourly during maintenance dose
- Respiratory rate, reflexes hourly
- Urine output (>100 mL over 4 hours)
- Fluid restrictions (80–85 mL/hour total fluid)

Fetal monitoring

- CTG (continuous if magnesium sulphate running)

Timing of birth

Any gestational age: Recommend birth after stabilising the woman and a course of corticosteroids (if ≤34+6 weeks) and magnesium sulphate for neuroprotection (if <30 weeks) has been completed (if time permits) – not required if already on magnesium sulphate

Intrapartum

- Frequent BP monitoring (eg, every 5–15 minutes) in labour. If on magnesium sulphate – follow protocol
- Continuous CTG
- Continue antihypertensives – adjust if necessary for other factors, eg, effect of magnesium sulphate, neuraxial anaesthesia

Postpartum

- Continue magnesium sulphate for 24 hours
- If on methyldopa, consider changing to another antihypertensive, eg, ACE inhibitor
- Continue to monitor for disease resolution, titrate antihypertensives as required
- Advise to stay in secondary/tertiary facility for at least 72 hours (4–6 hourly BP)
- Daily BP to 7 days after birth, then at least weekly to 6 weeks
- Give woman's GP a comprehensive discharge summary
- 6-week obstetric review

Antihypertensives for acute lowering of BP

Nifedipine

10 mg conventional release tablet (oral)

Onset: 30–45 minutes

Repeat: after 30–45 minutes (if needed)

Maximum: 80 mg daily

Labetalol

Initially 20 mg IV bolus over 2 minutes

Repeat with 40–80 mg

Onset: 5 minutes

Repeat with 40–80 mg

Repeat: every 10 minutes

Maximum: 300 mg

Hydralazine

5–10 mg (5 mg if fetal compromise)

IV bolus over 3–10 minutes

Onset: 20 minutes

Repeat: every 20 minutes

Maximum: 30 mg (consider IV bolus of crystalloid fluid before or when administering first IV hydralazine dose, usually 200–300 mL)

Magnesium sulphate

To prevent further eclamptic seizures, this anticonvulsant drug should be administered – **see protocol**

Pre-eclampsia bloods

- FBC
- Electrolytes
- Creatinine
- LFT (incl AST, ALT)
- Coagulation if AST, ALT abnormal/low platelets

Signs and symptoms of pre-eclampsia

- Severe headache
- Visual disturbances
- Severe epigastric pain
- Shortness of breath
- Retrosternal pressure/pain
- Nausea, vomiting
- Sudden swelling of face, hands or feet
- Hyperreflexia

ACE = angiotensin converting enzyme; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; CTG = cardiotocograph; FBC = full blood count; GP = general practitioner; IV = intravenous; LFT = liver function test; SpO₂ = saturation of peripheral oxygen

HELLP

A variant of severe pre-eclampsia.

Elements include Haemolysis, Elevated Liver enzymes and Low Platelet count

At diagnosis

- Immediately consult with obstetric team. Transfer of care (referral code 4006)
- BP control of primary importance if severe
- Admit to secondary/tertiary facility
- Spot urine PCR
- Pre-eclampsia bloods + coagulation bloods
- Assess fetal growth (umbilical artery Doppler assessment and cardiotocography if indicated)

Treatment

- Only conclusive treatment is birth of baby and placenta
- Begin magnesium sulphate – see protocol
- Start antihypertensive (acute), aim for a target BP below 140/100 mmHg

Maternal monitoring

- Management plan should include discussion with the woman, LMC, obstetric, anaesthetic and intensive care teams and physicians where appropriate
- At least daily pre-eclampsia bloods
- Conduct coagulation studies if you have concerns about possible placental abruption

Maternal monitoring – magnesium sulphate (if required)

- Blood pressure every 5 minutes during bolus dose then hourly during maintenance dose
- Respiratory rate, O₂ saturation, reflexes hourly
- Urine output (>100 mL over 4 hours)
- Fluid restrictions (replace loss at delivery and then 80–85 mL/hour total fluid)

Fetal monitoring

- CTG (continuous if magnesium sulphate running)

Timing of birth

Any gestational age: Recommend birth after stabilising the woman and a course of corticosteroids (if $\leq 34+6$ weeks) and magnesium sulphate for neuroprotection (if <30 weeks) has been completed (if time permits) – not required if already on magnesium sulphate

Intrapartum

- Frequent BP monitoring (eg, every 5–15 minutes) in labour. If on magnesium sulphate – follow protocol
- Continuous CTG
- Continue antihypertensives – adjust if necessary for other factors, eg, effect of magnesium sulphate, neuraxial anaesthesia

Postpartum

- Continue magnesium sulphate for 24 hours
- If on methyldopa, consider changing to another antihypertensive, eg, ACE inhibitor
- Continue to monitor for disease resolution, titrate antihypertensives as required
- Advise to stay in secondary/tertiary facility for at least 72 hours (4–6 hourly BP)
- Daily BP to 7 days after birth, then at least weekly to 6 weeks
- Give woman's GP a comprehensive discharge summary
- 6-week obstetric review

Antihypertensives for acute lowering of BP

Nifedipine

10 mg conventional release tablet (oral)

Onset: 30–45 minutes

Repeat: after 30–45 minutes (if needed)

Maximum: 80 mg daily

Labetalol

Initially 20 mg IV bolus over 2 minutes

Onset: 5 minutes

Repeat with 40–80 mg

Repeat: every 10 minutes (if needed)

Maximum: 300 mg

Hydralazine

5–10 mg (5 mg if fetal compromise)

IV bolus over 3–10 minutes

Onset: 20 minutes

Repeat: every 20 minutes

Maximum: 30 mg (consider IV bolus of crystalloid fluid before or when administering first IV hydralazine dose, usually 200–300 mL)

Pre-eclampsia bloods

- FBC
- Electrolytes
- Creatinine
- LFT (incl AST, ALT)
- Coagulation if AST, ALT abnormal/low platelets

Signs and symptoms of pre-eclampsia

- Severe headache
- Visual disturbances
- Severe epigastric pain
- Shortness of breath
- Retrosternal pressure/pain
- Nausea, vomiting
- Sudden swelling of face, hands or feet
- Hyperreflexia

ACE = angiotensin converting enzyme; ALT = alanine transaminase; AST = aspartate transaminase; BP = blood pressure; CTG = cardiotocograph; FBC = full blood count; GP = general practitioner; IV = intravenous; LFT = liver function test; LMC = lead maternity carer; O₂ = oxygen; PCR = protein: creatinine ratio

Magnesium sulphate

- Administering magnesium sulphate is clinically indicated to prevent another seizure in women with eclampsia, unless contraindicated.
Strong recommendation; high-quality evidence
- Also consider using magnesium sulphate to prevent a primary seizure in women with severe pre-eclampsia. However, the treatment priority is blood pressure control.
Weak recommendation; high-quality evidence
- Settings administering magnesium sulphate should have available one-on-one care, close monitoring and resuscitation/reversal medications (calcium gluconate).
Strong recommendation; very low-quality evidence
- For settings that cannot administer the full magnesium sulphate regimen, this guideline recommends using a loading dose intramuscularly (IM) or intravenously (IV) (see protocol) and then immediately transferring the woman to a higher-level health care facility.
Strong recommendation; low-quality evidence
- Continue magnesium sulphate for 24 hours following birth or 24 hours after the last seizure, whichever is the later.
Strong recommendation; very low-quality evidence
- Suggested loading dose and maintenance regime – see the magnesium sulphate protocol that follows.

Magnesium sulphate does not stop seizures but reduces the risk of a woman having a further seizure.

Eclamptic seizures are generally short-lived and self-limiting, so it is reasonable to delay administration of magnesium sulphate until the seizure has stopped.

Magnesium sulphate protocol

General information

Magnesium sulphate

- Magnesium sulphate is the drug of choice to prevent further seizures in women with eclampsia and to reduce the risk of seizures in women with severe pre-eclampsia.
- Magnesium sulphate is also used for neuroprotection of the fetus at gestation <30 weeks. This is not required if the woman is already having magnesium sulphate for HDP.
- Magnesium sulphate readily crosses the placenta.
- Magnesium is readily antagonised by IV calcium gluconate in the event of magnesium toxicity (calcium gluconate should be available where magnesium sulphate is used).

Indications

- As prophylaxis to minimise the risk of eclamptic seizures for women with severe unstable pre-eclampsia.
- To prevent further seizures in women with eclamptic seizures.

Precautions

Using this drug can be hazardous in association with:

- dosing errors
- renal failure or severe renal compromise
- hypocalcaemic states
- other drugs, especially vasoactive drugs
- acute haemolytic states.

Administration

- Magnesium sulphate is best administered intravenously. However, the intramuscular route may be appropriate in some situations.
- The product guidelines recommend diluting magnesium sulphate for intravenous use to a concentration of 20% magnesium or less.
- Intravenous administration of magnesium sulphate may be via a syringe driver or a volumetric infusion pump.

Care during intravenous infusion

- Collect baseline observations (pulse, blood pressure (BP), relative risk (RR), saturation of peripheral oxygen (SpO₂) and reflexes).
- Ensure the woman is aware that a feeling of warm flushing may be evident during the infusion. Other side effects may include nausea, vomiting and headache.
- Recheck observations including patellar or brachial reflexes (if neuraxial anaesthesia in place) 10 minutes after the loading dose starts and at the end of the loading dose (20 minutes).
- Continuously monitor the fetus from 26+0 weeks gestation until clinical review or discussion by medical staff. Between 24 to 26 weeks' gestation, consider individualised management related to fetal monitoring.

Maintenance

Monitor

- Monitor:
 - blood pressure – every 5 minutes during loading dose and then hourly during maintenance dose
 - respiratory rate/SpO₂ – hourly
 - patellar/brachial reflexes – hourly
 - urine output – review hourly (insert urine catheter). Should be >100 mL/4 hours
 - pre-eclampsia bloods = full blood count (including haemoglobin, platelet count), creatinine, electrolytes, liver function tests (albumin, ALT and AST).
- Document patellar or brachial reflexes (if neuraxial anaesthesia in place).
- Stop the infusion if:
 - reflexes are absent
 - the respiratory rate is less than 12 per minute, or
 - the urine output drops below 100 mL in 4 hours.
- Monitoring magnesium levels is usually not necessary. Where serum creatinine is >100 µmol/L or urine output is <100 mL over 4 hours, check serum magnesium levels and adjust infusion levels. In these circumstances, check serum magnesium levels every 6 hours after starting infusion and consider reducing rate of infusion to 0.5 G/hour.
 - Do **not** take blood for estimating magnesium from the arm receiving the infusion.
 - Levels will vary according to serum albumin concentrations.
 - Carefully monitor patients with chronic kidney disease or renal impairment because magnesium and calcium accumulation is more likely in these patients.

Toxicity

If signs of toxicity occur (hypoventilation, arrhythmia, hypotonia):

- call for medical assistance
- administer oxygen at 8–12 litres/minute
- stop infusion
- monitor vital signs
- administer calcium gluconate (10% solution), 10 mL, slowly intravenously
- check electrolytes, creatinine and magnesium sulphate levels.

Magnesium sulphate IV regimen

- The total adult daily dose should be no more than 40 g of magnesium sulphate.
- Do not administer more than 8 g of magnesium sulphate over 1 hour.
- Continue for 24 hours following birth or 24 hours after the last seizure, whichever is the later.

To prevent eclampsia (prophylaxis)

- For the loading dose, administer 4 g over 10 minutes. (Dilute to local protocol. Concentration should be no higher than 20%.)
- After 10 minutes, use maintenance dose infusion to begin maintenance at 1 g/hour.
- Conduct electrocardiogram (ECG) monitoring and notify anaesthetist.

For eclamptic seizures

- For the loading dose, administer 4 g over 5–10 minutes. (Dilute to local protocol. Concentration should be no higher than 20%.)
- After 10 minutes, use maintenance dose infusion to begin maintenance at 1 g/hour.
- Conduct ECG monitoring and have anaesthetist on site.
- If seizures have not stopped, an alternative medication may be required.

When seizure recurs during maintenance treatment

- Administer 2 g IV over 10 minutes. (Dilute to local protocol. Concentration should be no higher than 20%.)
- Once the condition is stable, either:
 - reset volumetric infusion pump to maintenance dose of 1 g/hour
 - increase the maintenance infusion rate to 2 g/hour.
- Check for hyporeflexia and reduced respiration rate.

Ensure calcium gluconate is available.

Intramuscular dose (suitable for retrieval and transfer)

If IV administration is not available, an intramuscular magnesium sulphate 50% may be preferable for treating women with severe unstable pre-eclampsia.

The preferred regimen in such circumstances is to:

- administer two deep intramuscular injections of 4 g magnesium sulphate 50% solution into each buttock (the total dose of up to 10 g injected into one site is highly irritating)
- provide maintenance treatment of 5 g magnesium sulphate 50%, given by deep intramuscular injection, every 4 hours
- alternate the buttocks in which you administer the injection
- begin a maintenance infusion (see above) at any time after the initial bolus dose but, in this circumstance, consider measuring blood levels of magnesium.

Facilities differ in their protocols for compounding and administering magnesium sulphate infusions. No evidence is available to support the best way to do this. However, this guideline has sourced guidance from an article from the Director of Error Reporting Programs at the Institute for Safe Medication Practices, which was developed from reported errors when administering magnesium sulphate for obstetric purposes.^{23, 24}

Practice points for administering IV magnesium sulphate

- Premixed solutions. Staff should not have to mix magnesium sulphate solutions. Settings should make available premixed solutions for bolus doses and maintenance infusions. Avoid non-standard concentrations. Give bolus doses in separate, premixed piggyback infusions; do not administer them from the maintenance infusion.
- Label lines. When starting infusions or adjusting the rate, trace the tubing by hand from the IV bag, to the pump, and then to the patient for verification.
- Protocols. Establish dosing and administration protocols and standard order sets for magnesium sulphate.
- Double-checks. Make it a requirement to have an independent double-check of the drug, concentration, infusion rate, pump settings, line attachment, and patient before administering IV magnesium sulphate.
- Monitoring. Monitor the patient's vital signs, oxygen saturation, reflexes, and level of consciousness as outlined above. Assess the patient regularly for signs of toxicity as above. During bolus administration, a staff member should remain at the woman's bedside to oversee continuous monitoring.
- Staffing ratios. Staffing patterns should be sufficient to allow time for proper monitoring.
- Emergency preparedness. Educate staff to respond to emergencies caused by overdoses. Calcium gluconate should be readily available.

3. Intrapartum

This section covers the period immediately before and during birth. The first consideration in the intrapartum management of hypertensive disorders in pregnancy should be the safety of the woman and her fetus. The second is to have a birth of a mature newborn that will not require intensive or prolonged neonatal care. Pre-eclampsia is a progressive disease; the ultimate treatment is to deliver the baby and placenta.

Timing

In deciding on the timing of the birth, consider blood pressure level and its treatment, potential complications linked with the chosen mode of birth, the health of the mother and fetus, other obstetric complications or co-morbidities, and the woman's preferences.

For women with chronic hypertension

- **Before 37 weeks:** Do not recommend birth unless other maternal or fetal indications support it.
Strong recommendation; moderate-quality evidence
- **After 37 weeks:** For women with low risk of adverse outcomes, consider expectant management beyond 37 weeks with increased monitoring.
Strong recommendation; moderate-quality evidence

For women with gestational hypertension

- **Before 37 weeks:** Recommend expectant management. Do not recommend birth unless other maternal or fetal indications support it.
Strong recommendation; moderate-quality evidence
- **After 37 and before 40 weeks:** Consider birth. The woman, her LMC and the obstetric team should negotiate the timing.
Strong recommendation; moderate-quality evidence

For women with pre-eclampsia who are stable and without severe features

- **Before 37 (eg, 36+6) weeks:** Adopt an expectant approach. Do not recommend birth if no other maternal indicators (eg, premature rupture of membranes, preterm labour or vaginal bleeding, deterioration of condition) or fetal indications support it. Usually you should manage this condition with the woman as an inpatient.
Strong recommendation; moderate-quality evidence
- **After 37 (eg, 37+0) weeks:** Recommend birth. Continuing pregnancy after 37 weeks has no appreciable benefits and increases the risk of deterioration. Decide on the timing and method after discussion with the woman, her LMC and the obstetric team.
Weak recommendation; low-quality evidence

For women with severe/unstable pre-eclampsia

- **Peri- or pre-viability:** Manage the condition in a tertiary setting in consultation with maternal fetal medicine if possible, and with careful discussion with the woman.
Strong recommendation; moderate-quality evidence
- **Before 34 weeks:** Adopt an expectant approach in a secondary or tertiary centre with resources for maternal and fetal monitoring and critical care of the mother and the baby. If indication for birth presents, administer corticosteroids for fetal lung maturation and magnesium sulphate for fetal neuroprotection (if <30 weeks).
Strong recommendation; moderate-quality evidence
- **After 34 weeks:** Recommend birth after stabilising the woman in a centre with appropriate resources to care for the mother and the baby.
Strong recommendation; low-quality evidence

For women with HELLP or eclampsia

- **Any gestational age:** Recommend birth after stabilising the woman and after she has completed a course of corticosteroids ($\leq 34+6$ weeks) and magnesium for neuroprotection (if <30 weeks) (if time permits).
Strong recommendation; moderate-quality evidence

Anaesthesia

- It is possible to use neuraxial methods of analgesia (ie, spinal, epidural and combined spinal and epidural anaesthesia (CSE)) in labour safely, even for women with lower platelet counts. However, this guideline does not generally recommend using them when the platelet count is $<80 \times 10^9/L$.
Strong recommendation; low-quality evidence
- Fluid preloading is not required when siting neuraxial anaesthetics.
Strong recommendation; very low-quality evidence
- Spinal anaesthesia and CSE are the preferred techniques for caesarean section if an epidural is not already in place.
Strong recommendation; very low-quality evidence

☑ Neuraxial anaesthesia is less likely to cause hypotension in pre-eclamptic women than in healthy women, but it may still occur.

- If general anaesthesia is necessary, rapid sequence induction is the preferred technique. Aggressively prevent the hypertensive response to intubation.
Strong recommendation; low-quality evidence
- Propofol is safe and effective as an induction agent for general anaesthesia.
Weak recommendation; very low-quality evidence
- Central venous pressure monitoring is not usually required and may be harmful.
Strong recommendation; very low-quality evidence
- This guideline does not recommend pulmonary artery catheterisation.
Strong recommendation; very low-quality evidence
- A peripheral arterial line is not required in pre-eclampsia but can be useful for monitoring blood pressure.
Strong recommendation; very low-quality evidence
- Magnesium sulphate can continue during caesarean section.
Strong recommendation; low-quality evidence
- Fluid restriction is advisable to reduce the risk of fluid overload in the intrapartum and postpartum periods. Pulmonary oedema has been a significant cause of maternal death in eclampsia and pre-eclampsia, often linked with administering excess fluid. Usually limit total fluids to 80–85 mL/hour for severe pre-eclampsia.
Strong recommendation; low-quality evidence

☑ A good working epidural in labour for a woman with a severe hypertensive disorder in pregnancy can be useful to help reduce the hypertensive response to labour pain, but also can easily be topped up if a caesarean section follows. This may avoid the need for a general anaesthetic in an emergency. Consider potential side effects and the woman's choice before opting for an epidural.

Mode of birth

- The preferred mode of birth is always vaginal unless it is contraindicated for the mother or the fetus. Eclampsia is not an indication for caesarean section. In many cases, induced labour is a safe option.
Weak recommendation; low-quality evidence
- Vaginal birth is often possible in women with pre-eclampsia or eclampsia. Evidence shows neonatal outcomes are better even if an induction ends in caesarean than they are from an elective caesarean at many gestations.
Strong recommendation; moderate-quality evidence
- Make the decision about mode of birth with the woman and the medical team (including obstetrics, neonatology and anaesthetics).
Weak recommendation; very low-quality evidence
 - Make vaginal birth with or without-induction the preferred choice in women with pre-eclampsia but no other obstetric contraindications.
 - Before 28 weeks of gestation, however, labour induction is less successful and maternal and fetal disease is likely to be more severe. Consider caesarean section for this reason.
- Actively managing the third stage of labour is clinically indicated in women with hypertensive disorders in pregnancy.
Strong recommendation; very low-quality evidence
- Avoid ergometrine and Syntometrine® as an uterotonic in women with hypertensive disorders except when massive obstetric haemorrhage occurs.
Weak recommendation; very low-quality evidence

4. Postpartum

Postpartum consequences can be lifelong for women who have experienced a hypertensive disorder in pregnancy. This section covers the immediate period after birth followed by long-term considerations and recommendations.

Postnatal monitoring

- Carefully monitor women with hypertensive disorders in pregnancy for increasing hypertension postpartum. Blood pressure frequently increases about three to five days after birth. Continue to monitor blood pressure frequently through the postnatal period (see Table 3).
Strong recommendation; very low-quality evidence
- Continue to observe strict fluid balance in women with severe pre-eclampsia.
Weak recommendation; low-quality evidence
- Monitor for all signs of pre-eclampsia (including pre-eclampsia bloods) returning to normal but beware of post-partum eclampsia.
Strong recommendation; high-quality evidence

Mental health screening and debriefing

Women may have ongoing mental health issues after an experience of a complex pregnancy. This experience can be frightening for the woman and her family and whānau.

- Normal screening for postnatal depression is imperative. A woman may need additional support because she is more likely to have post-traumatic stress disorder and depression after experiencing severe hypertension or pre-eclampsia in pregnancy.
Strong recommendation; very low-quality evidence
- Give women the opportunity to debrief after experiencing hypertension or pre-eclampsia in pregnancy. Discuss what this means for future pregnancies and their long-term health.
Strong recommendation; very low-quality evidence

Long-term risks

- Give women with a history of hypertensive disorders in pregnancy information on long-term risks of pre-eclampsia, including cardiovascular disease, and the importance of following a healthy lifestyle. (See Table 4 for a list of these risks.)
Strong recommendation; very low-quality evidence
- Give women with a history of pre-eclampsia information on risks linked with subsequent pregnancies. Give them the opportunity to discuss contraceptive options, if they wish to.
Weak recommendation; very low-quality evidence

✓ Most of the commonly used antihypertensive drugs appear to be safe for the baby. The benefits of breastfeeding outweigh potential risks to the baby of transfer of antihypertensive drugs in breast milk. Preterm babies may be more susceptible to these risks.

✓ Women with hypertensive disorders in pregnancy are at higher risk of venous thromboembolism. Assess the need for preventive treatments, using a recognised risk assessment tool.

✓ Send a comprehensive discharge summary to the woman's primary carers (eg, LMC and GP) and the woman. This is particularly important for arranging long-term, ongoing follow-up.

✓ Many women are unaware of the long-term health implications of pre-eclampsia. Explain these implications and take the time to be sure each woman fully understands them.

- Assess women with a history of pre-eclampsia every year for blood pressure, lipids, blood glucose, thyroid function and body mass index (BMI). Long-term risks appear to increase significantly 10 years after the initial hypertensive event. Take this timing into account when advising women on ongoing surveillance for these risks.

Weak recommendation; very low-quality evidence

Table 4: Risk of developing long-term conditions for women who have had gestational hypertension or pre-eclampsia

Future risk	Hypertensive disorder in index pregnancy	
	Gestational hypertension*	Pre-eclampsia
	Relative risk (95%CI)	
Gestational hypertension in future pregnancy	3.4 (2.0–5.8) ²⁵	6.3 (3.4–12.0) ²⁵
Pre-eclampsia in future pregnancy	7.57 (2.31–24.78) ²⁶ **	7.19 (5.85–8.83) ²²
Chronic hypertension	3.39 (0.82–13.9) ²⁷	3.13 (2.51–3.89) ²⁸
Cardiovascular disease	1.66 (0.62–4.41) ²⁷	2.28 (1.87–2.78) ²⁸
Cerebrovascular disease	1.47(1.05–2.0) ²⁹	1.76(1.43–2.21) ²⁷
Venous thromboembolism	-	1.79 (1.37–2.33) ²⁷
End-stage kidney disease	-	4.3 (3.3–5.6) ³⁰

* More research is required around the long-term effects of gestational hypertension.

** Odds ratio

CI = confidence interval.

Evidence statements

This section provides evidence statements that respond to each clinical question. The GDT used these statements to make the recommendations related to those questions (which are also presented here) and provide key information such as:

- a summary of available data on all important outcomes
- the quality of evidence
- the magnitude of effect of the interventions examined
- the applicability of the results
- other information, such as considerations of harms, costs and current practice.

The supplementary tables' document provides evidence profile tables, where possible. These present key data from systematic reviews, meta-analyses and randomised controlled trials. Alternatively, if a study could not be included in an evidence profile table, the supplementary tables' document summarises and presents it in the 'other evidence tables'. Where this section refers to tables and evidence profiles that are not included in this section, it is referring to tables and evidence profiles in the supplementary tables' document. (See Appendix A for further details on methods.)

Evidence statement: Classifications and clinical definitions

Introduction

The purpose of classifying hypertensive disorders in pregnancy and defining related terms is to create clear categories that reflect the risks and potential outcomes for the pregnant woman and her baby and so guide clinical management. Clear classifications also enable accurate record keeping and help with research aimed at improving outcomes for women and babies. While existing clinical practice guideline* on the topic differ in the range of conditions they include in classifying and defining hypertensive disorders in pregnancy, those differences are few.^{31, 32, 33, 34, 35} Where guidelines differ, the GDT has used expert opinion, such as the statements from expert groups from the ISSHP, as guidance.¹

Classification of hypertensive disorders in pregnancy

This guideline classifies hypertensive disorders in pregnancy in line with the 2014 revised ISSHP statement as:

1. chronic/pre-existing hypertension
2. gestational hypertension
3. pre-eclampsia – de novo or superimposed on chronic hypertension
4. eclampsia
5. HELLP syndrome (see below for the definition of each of these conditions).

Note

Several guidelines do not include postpartum hypertension in classifying hypertensive disorders in pregnancy. However, studies have recognised that, in addition to the peak rise in blood pressure between the third and fifth day postpartum, new onset hypertension can develop from two weeks to six months after birth.^{33,36} For this reason, although this guideline does not specifically include the condition in its classification, it draws attention to the conditions classified as hypertensive disorders in pregnancy in the postpartum period.³⁷

Hypertension

Systolic blood pressure is greater than or equal to 140 mmHg **or** diastolic blood pressure is greater than or equal to 90 mmHg, as measured on two or more consecutive occasions at least four hours apart.

Chronic/pre-existing hypertension

Hypertension is confirmed before conception or before 20 weeks of gestation with or without a known cause, as measured on two or more consecutive occasions at least four hours apart.

Gestational hypertension

The new onset of hypertension occurs after 20 weeks' gestation (in a woman who had normal blood pressure before 20 weeks of gestation) and:

- diastolic blood pressure is ≥ 90 mmHg **or** systolic blood pressure is ≥ 140 mmHg
- the woman has none of the abnormalities that define pre-eclampsia
- her blood pressure returns to normal within three months after giving birth.

* Guidelines reviewed for definitions are: ACOG (American College of Obstetricians and Gynecologists), ADHB (Auckland DHB guidelines), CDHB (Canterbury DHB guidelines), NICE (National Institute for Health and Clinical Excellence, UK), QLD (Queensland clinical guidelines), SOMANZ (Society of Obstetric Medicine of Australia and New Zealand), SOGC (Society of Obstetricians and Gynaecologists of Canada), ESC (European Society of Hypertension & European Society of Cardiology) and ISSHP (International Society for the Study of Hypertension in Pregnancy).

White coat hypertension

Hypertension occurs in a clinical setting while blood pressure is normal in a non-clinical setting when assessed by 24-hour ambulatory blood pressure monitoring or home blood pressure monitoring using an appropriately validated device.

Degrees of hypertension

- Mild/moderate hypertension is when diastolic blood pressure is 90–109 mmHg **or** systolic blood pressure is 140–159 mmHg.
- Severe hypertension is when diastolic blood pressure is 110 mmHg or greater **or** systolic blood pressure is 160 mmHg or greater.

Notes

In the various definitions of severe hypertension, the reference to cut-off levels in systolic blood pressure differs in existing clinical practice guidelines and in research. Some guidelines use a reference of 160 mmHg while others use 170 mmHg systolic blood pressure to define severe hypertension.^{31,32,33,34,38} This guideline uses systolic blood pressure of 160 mmHg or greater to be consistent with the ISSHP definition.³⁹

On the practice of taking two consecutive measurements at least four hours apart, expert opinion is that such a strategy may lead to delay in appropriate care for severe hypertension. Therefore, in severe hypertension, use your clinical judgement on measuring more frequently (eg, every 15 minutes and then every 30 minutes in the initial phase of assessment).^{32,38}

Pre-eclampsia

The new onset of hypertension occurs after 20 weeks' gestation (in a woman who had normal blood pressure before 20 weeks' gestation) or superimposed on pre-existing hypertension **and one or more** of the following also develop as new conditions:

1. proteinuria – spot urine protein:creatinine ratio ≥ 30 mg/mmol or $\geq 2+$ on dipstick testing confirmed by a protein creatinine ratio test
2. other maternal organ dysfunction:
 - renal insufficiency (creatinine >90 $\mu\text{mol/L}$, urine output of $<80\text{mL/4hr}$)
 - liver involvement – elevated transaminases (ALT & AST) – at least twice upper limit of normal \pm right upper quadrant or epigastric abdominal pain). Note normal ranges are: ALT 0-30 u/L and AST 10-50 u/L
 - neurological complications (eg, eclampsia, altered mental status, blindness, stroke or, more commonly, hyperreflexia when accompanied by clonus, severe headaches and persistent visual scotomata)
 - haematological complications (thrombocytopenia – platelet count below $100 \times 10^9/\text{L}$, haemolysis)
3. uteroplacental dysfunction (fetal growth restriction).

Each of the following is a **severe feature of pre-eclampsia**:

- severe hypertension (dbp ≥ 110 mmHg **or** sBP ≥ 160 mmHg)
- worsening of **thrombocytopenia** (platelet count less than $100 \times 10^9/\text{L}$)
- **impaired liver function** not responding to treatment and not accounted for by alternative diagnosis – elevated transaminases (AST and ALT) – at least twice the upper limit of normal \pm right upper quadrant or epigastric abdominal pain (may be referred to upper back)

- **progressive renal insufficiency** (serum creatinine >90 µmol/L or doubling of serum creatinine concentration in the absence of other renal disease, urine output of <80 mL/4hr)
- pulmonary oedema
- new onset of headaches and visual disturbances
- HELLP syndrome
- eclampsia.

Unstable pre-eclampsia

Women with pre-eclampsia who have worsening pre-eclampsia blood results and severe hypertension not easily controlled with antihypertensives. This condition is also known as fulminating pre-eclampsia.

The high maternal and fetal morbidity and mortality associated with pre-eclampsia supports efforts to more closely monitor symptoms of severe features to guide management and referral. Once severe features develop, it would seem prudent to recommend managing these women at least initially as inpatients in a centre with a maternal and neonatal high-dependency or intensive care unit.⁵

Notes

Severity of proteinuria: The issue of the severity of proteinuria is critical as there is no clear evidence or consensus on what amount of proteinuria is 'severe'.^{38,39} Although the majority of current guidelines on pre-eclampsia rely on values between 3 and 5 g/L, the current evidence shows that no association between the level of proteinuria and progression of the disease.^{40,41} The current recommendations for clinical practice state that the amount of proteinuria should **not** be a criterion of severity of pre-eclampsia and so do not support repeat testing of proteinuria once it has been established.^{31,32,33,34,35}

Fetal growth restriction: The historical view of worsening fetal growth restriction was that it is a severe feature of pre-eclampsia. However, because the management of fetal growth restriction is similar in non-pre-eclamptic women, the current opinion is not to include fetal growth restriction as a severe feature of pre-eclampsia.³⁴

Proteinuria: Although proteinuria is the most common feature of pre-eclampsia that distinguishes it from gestational hypertension,⁴² the current evidence suggests that proteinuria is not an absolute requirement for establishing the diagnosis of pre-eclampsia.^{31, 32, 36, 39} This is based on the evidence that non-proteinuric pre-eclampsia occurs in 25% of cases and the outcome profile is comparable between pre-eclamptic women with proteinuria and those with other pre-eclamptic features, including those with hypertension and fetal growth restriction in the absence of proteinuria.^{40,41} So it is possible to diagnose pre-eclampsia after establishing a woman has hypertension and new onset proteinuria **or** when she has no proteinuria but hypertension is linked with new onset thrombocytopenia, impaired liver function, renal insufficiency, pulmonary oedema, or visual or cerebral disturbances.

Quantification of proteinuria: For quantification of proteinuria, guidelines have more frequently used 24-hour urine protein >300 mg/day. However, this approach has pitfalls in clinical practice and is time consuming. On the other hand, studies have noted a spot urine protein:creatinine ratio ≥30 mg/mmol has adequate sensitivity and specificity to be the optimal measurement for ruling out or confirming proteinuria.^{39,43} Although a dipstick can alert clinicians to an initial diagnosis, it has poor sensitivity (range from 22–28%) and evidence shows it improves marginally with automated dipstick tests.^{44,45,46} So the presence of 2+ or 3+ in a dipstick indicates the presence of proteinuria, but it is not adequate to confirm or rule out proteinuria. The recommended method for confirming it is to use the spot urine protein:creatinine ratio.^{31,32}

Renal insufficiency: Because research shows the serum:plasma creatinine ratio falls during pregnancy, levels at the upper limit of normal range (70–100 µmol/L) are considered to indicate impaired renal function.⁴⁷ However, there is no consensus on the cut-off levels to be considered in diagnosing pre-eclampsia. Current recommendations use >90 µmol/L or >100 µmol/L.^{1, 31,32,33,}

Oliguria: Usually the definition of oliguria is based on the 24-hour urine output. However, as disease progression can occur very quickly in pre-eclamptic women, the recommended method for diagnosing it is observation over four hours and measurement of a urine output of <80 mL/4 hours.^{1, 31}

Liver involvement: The recommended criterion of liver involvement is that the patient has raised transaminases (abnormal blood concentrations twice that of normal concentrations) with or without severe epigastric or right upper quadrant pain.^{1, 31,32,38}

Neurological involvement: The criteria of neurological involvement are based on clinical symptoms and examination.^{31,32,33,34} Examples include eclampsia, altered mental status, blindness and stroke; more common are hyperreflexia when accompanied by clonus, severe headaches and persistent visual scotomata.

Haematological complications: The lower limit of the normal platelet count in pregnancy is <150 × 10⁹/L.^{31,48} However, other existing clinical practice guidelines use the cut-off level for an abnormal platelet count in pre-eclampsia as <100 × 10⁹/L.^{31,32,33,34} The ISSHP's cut-off level in the diagnostic criteria of pre-eclampsia (<150 × 10⁹/L) differs from the level for HELLP (<100 × 10⁹/L).^{1,39} It is likely that differences arise from different classification systems used for HELLP.^{49, 50}

Indications of haemolysis include red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase (LDH) >600 IU/L, and decreased haptoglobin.^{32,34}

Hyperuricemia: The evidence suggests that serum uric acid levels may help differentiate those who will develop pre-eclampsia from those with simple gestational hypertension; and possibly, among pre-eclamptic women, those with a worse prognosis.^{51, 52, 53} The current evidence on effectiveness of serum uric acid concentration in managing pre-eclampsia is conflicting and inadequate to recommend its clinical use in diagnosing pre-eclampsia or progression of the disease.⁵⁴ Note that Māori have a statistically significantly higher prevalence of hyperuricaemia (serum units >0.40 mmol/L) compared with non-Māori (17.0% vs 7.5%, p = 0.0003).⁵⁵

Alternative diagnoses: Certain alternative diagnoses have some features of pre-eclampsia, such as acute fatty liver of pregnancy, haemolytic uremic syndrome, thrombotic thrombocytopenic purpura, exacerbation of systemic lupus erythematosus and cholecystitis.⁵⁶

Eclampsia

New onset of seizures occurs in association with pre-eclampsia. It is a severe manifestation of pre-eclampsia and can occur before, during or after birth. It can be the presenting feature of pre-eclampsia in some women.

Note

Up to 44% of eclamptic seizures occur after birth.⁵⁷ Other causes of seizures include a bleeding arteriovenous malformation, ruptured aneurysm, epilepsy or idiopathic seizure disorder. These alternative diagnoses may also be associated with the new onset of seizures occurring 24–72 hours after birth.^{32,34}

HELLP syndrome

A variant of severe pre-eclampsia (elements include **H**aemolysis, **E**levated **L**iver enzymes and **L**ow **P**latelet count). In a woman with pre-eclampsia, the presence of any of the following is an indicator of HELLP:

- maternal platelet count of less than $100 \bar{u} \times 10^9/L$
- elevated transaminases (abnormally elevated blood concentrations of liver enzymes to twice the normal concentration)
- microangiopathic haemolytic anaemia with red cell fragments on blood film.

Diagnostic testing

The evidence for angiogenic factors is not yet sufficient to recommend using them as a diagnostic tool or to define or classify hypertensive disorders in pregnancy.

Evidence statement: Risk factors

Risk factors for pre-eclampsia – recommendations

- As part of a comprehensive health assessment at booking, review all women for the risk factors for pre-eclampsia (Table 5). This will help to appropriately identify those women who are most at-risk. Women who have a major risk factor (MRF) have an approximately 20% risk of developing pre-eclampsia and should be considered as high risk.¹²

Strong recommendation; low-quality evidence

- Models are currently insufficient to determine a cumulative increase in risk of pre-eclampsia if a woman has multiple risk factors. However, give special consideration to a woman with several risk factors.

Weak recommendation; high-quality evidence

Table 5: Increased risk of developing pre-eclampsia if woman has pre-existing risk factors

Pre-existing risk factor	Relative risk/ odds ratio	95% CI	Notes
Antiphospholipid antibodies/SLE	9.72 ^b	4.34–21.75	MRF
Previous history of pre-eclampsia	7.19 ^b	5.85–8.83	MRF
ART (oocyte donation) ¹³	4.34 ^a	3.10–6.06	MRF
Renal disease ¹⁴	4.07 ^a	2.17–7.66	MRF
Chronic hypertension	3.6 ^a	2.0–6.6	MRF
Previous history of HELLP	3.7 ^a	0.9–16.1	MRF
Pre-existing diabetes	3.56 ^b	2.54–4.99	MRF
Family history of pre-eclampsia in mother or sister	3.3	1.5–7.4	MRF
Genetic ancestry – African ¹⁶	2.97 ^a	1.98–4.4	
– Indian	2.66 ^a	1.29–5.48	
– Māori ¹⁷	1.51 ^a	1.16–1.96	
– Pacific	1.21 ^a	0.99–1.57	
Nulliparity	2.91 ^b	1.28–6.61	
Multiple pregnancy	2.93 ^b	2.04–4.21	
Family history of pre-eclampsia Father of baby ¹⁸	2.9 ^a 2.1	1.70–4.93 1.0–4.3	
Change in partner ¹⁹	2.5 ^b	1.8–3.5	
Elevated BMI ≥35 (pre-pregnancy)	2.47 ^a	1.78–3.15	
Maternal age ≥40 – multiparous	1.96 ^b	1.34–2.87	
– primiparous	1.68 ^b	1.23–2.29	
Pregnancy interval >10 years	1.83 ^b	1.72–1.94	
ART (sperm donation) ²⁰	1.63 ^a	1.36–1.95	
Diastolic BP ≥80 mmHg at booking	1.38 ^b	1.01–1.87	
Any ART ²¹	1.17 ^a	1.10–1.24	

a. Adjusted odds ratio. b. Relative risk. Data from Duckitt & Harrington (2005)²² unless otherwise referenced

ART = assisted reproductive technology; BMI = body mass index; BP = blood pressure; CI = confidence interval; HELLP = Haemolysis, Elevated Liver enzymes and Low Platelet count; MRF = major risk factor; SLE = systemic lupus erythematosus.

Introduction

The evidence on risk factors comes from observational studies. It shows that the risk of pre-eclampsia is increased in women with a history of hypertensive disorders in a previous pregnancy or a family history, pre-existing medical conditions, and personal and pregnancy specific factors.^{17,22,58} The relative risk (RR) or odds ratio (OR) that should be considered against the background risk is estimated to be 4–5% nulliparous and 2–3% in low-risk multiparas.³ It is important to identify risk factors early so that the woman can then receive appropriate monitoring and treatment.

Previous history of hypertensive disorders and chronic hypertension

A review of 52 cohort studies demonstrated that women who had pre-eclampsia in a first pregnancy have seven times the risk of pre-eclampsia in a second pregnancy (unadjusted RR 7.19, 95% CI 5.85–8.83 from all studies; and 7.61, 95% CI 4.30–13.47 from case-control studies). Having a history of HELLP syndrome more than triples this risk (adjusted OR 3.7; 95% CI 0.9 – 16.1).¹⁵

One study (536 women) demonstrated that among women who developed pre-eclampsia, the prevalence of chronic hypertension was higher than among women who did not (12.1% vs 0.3%). Another study (of 155 women) observed that women with chronic hypertension with superimposed pre-eclampsia had significantly higher rates of adverse fetal outcomes (perinatal morbidity (OR 8.8; 95% CI 2.6–39.0), small for gestational age infants (OR 5.6; 95% CI 1.8–16.0) and birth before 32 weeks (OR 15.0; 95% CI 5.7–38.0)) compared with women with chronic hypertension without superimposed pre-eclampsia⁵⁹ (see Risk factors other evidence table).

Family history

Having a family history of pre-eclampsia nearly triples the risk of pre-eclampsia (unadjusted RR 2.90, 95% CI 1.70–4.93 from all studies; and 3.60, 95% CI 1.49–8.67 from case-control studies)²² (see Risk factors tables 1 and 2). In this review, family history focused on the mother of the pregnant woman.²² However, other studies and ongoing research indicate that a family history should include the woman's sister: relative risk of family history (mother or sister) positive vs family history negative for total pre-eclampsia = 3.4 (95% CI 1.5–7.6; $p = 0.018$); severe pre-eclampsia = 4.3 (95% CI 1.6–11.5; $p = 0.017$).⁶⁰ Another study found that women with pre-eclampsia were 2.3 times (95% CI 1.8–2.9) more likely to have a sister who had pre-eclampsia; those with gestational hypertension were 1.6 times (95% CI 1.3–2.0) more likely to have a sister with gestational hypertension.⁶¹

Female relatives of the father of the baby may also need to be considered as, where the father of a baby had a mother who had had pre-eclampsia and he, himself, was the product of a pregnancy complicated by pre-eclampsia, the odds ratio was 2.1 (95% CI 1.0–4.3; $p = 0.04$).¹⁸ For an aetiology of these findings, see a review by Dekker et al.⁶² Ongoing genetic research, including Australasian studies, also support this evidence.⁶³

Pre-existing medical conditions

The evidence shows that a woman is almost four times more likely to develop pre-eclampsia if she had diabetes (insulin dependent) before pregnancy (unadjusted RR 3.56, 95% CI 2.54–4.99). The prevalence of renal disease is higher in women who develop pre-eclampsia compared with those that do not (unadjusted OR 4.07, 95% CI 2.17–7.66).¹⁴ A systematic review found that the overall incidence of adverse maternal events is five times higher in women with chronic kidney disease (CKD) compared with women without CKD.⁶⁴

The evidence from a matched case-control study in a systematic review indicates that women with autoimmune disease (the presence of anticardiolipin antibodies or lupus anticoagulant or both) significantly increases the risk of developing pre-eclampsia (unadjusted RR 9.72, 95% CI 4.34–21.75). However, this review observed that when women who developed pre-eclampsia were matched with women who did not, they were no more likely to be positive for lupus anticoagulant or anticardiolipin antibodies²² (see Risk factors table 1 and Risk factors other evidence table).

Factors related to the individual woman and the pregnancy

Age

Women aged ≥ 40 years had almost twice the risk of developing pre-eclampsia, whether they were primiparous (unadjusted RR 1.68, 95% CI 1.23–2.29) or multiparous (unadjusted RR 1.96, 95% CI 1.34–2.87). Younger maternal age did not seem to affect the risk of developing pre-eclampsia²² (see Risk factors table 1).

Ethnicity

A study of 26,254 women in New Zealand demonstrated a univariate association with ethnicity. The evidence showed that, compared with European women, the risk of pre-eclampsia is nearly 50% lower among Chinese women (adjusted OR 0.56, 95% CI 0.41–0.76) and nearly 50% higher for Māori women (adjusted OR 1.51, 95% CI 1.16–1.96); the risk is also higher for Pacific women (OR 1.44, 95% CI 1.20–1.74) and Indian women (OR 1.35, 95% CI 1.05–1.73)¹⁷ (see Risk factors table 3). Another study in the United Kingdom observed that Black women had a higher risk of early onset pre-eclampsia compared with White women (adjusted OR 3.64, 95% CI 1.84–7.21)¹⁶ (see Risk factors table 4).

BMI

The systematic review of case-controlled and cohort studies demonstrated that a high body mass index (BMI) was associated with a 50% higher risk of pre-eclampsia, and that a pre-pregnancy BMI ≥ 35 more than doubles the pre-eclampsia risk (unadjusted RR 2.47, 95% CI 1.66–3.67).²² One study in this review noted that the risk of pre-eclampsia was significantly reduced with a BMI < 20 (OR 0.76, 95% CI 0.62–0.92, adjusted for diabetes and smoking). Another retrospective cohort study of nulliparous women found that any woman with excessive weight gain, but especially those with high BMI, (in relation to Institute of Medicine guidelines⁶⁵) and ≥ 9 kg gain, were more likely to have adverse maternal outcomes (pre-eclampsia: adjusted odds ratio (AOR) 2.78, 95% CI 2.82–2.93; eclampsia: AOR 2.51, 95% CI 2.27–2.78).⁶⁶ Note too that a study of Chinese women found that the impacts of high BMI on pre-eclampsia (as well as gestational diabetes and preterm delivery) might be stronger for them than for Caucasian women.⁶⁷

All of this evidence points to the importance of appropriate gestational weight gain in pregnancy to reduce the risk of developing hypertensive disorders and other pregnancy complications. (See Risk factors other evidence table.)

Previous births

The evidence also shows that parity has a ‘U’-shaped univariate association with higher risk of pre-eclampsia in nulliparous women and women with parity of 3 or more, and that nulliparity almost triples the risk for pre-eclampsia (unadjusted RR 2.91, 95% CI 1.28–6.61).²² The longer interval of more than 10 years between pregnancies was also associated with a significantly higher risk of pre-eclampsia in a second pregnancy when pre-eclampsia had not been present in the first pregnancy. However, when the interval was 10 years or less, the risk of pre-eclampsia was about the same as that in nulliparous women.^{22,68} After adjusting for the presence or absence of a change of partner, maternal age

and year of birth, the risk of pre-eclampsia increases for each one-year increase in the interval between births (OR 1.12, 95% CI 1.11–1.13)⁶⁸ (see Risk factors other evidence table).

Change in paternity has also been associated with increased risk of pre-eclampsia. Studies show a 29% adjusted attributable risk of pre-eclampsia in multiparas associated with a change in paternity (adjusted OR 1.3, 95% CI 1.1–1.6)¹⁹ (see Risk factors table 5).

Twin pregnancies

In twin pregnancies, the risk of pre-eclampsia nearly triples (unadjusted RR 2.93, 95% CI 2.04–4.21).²²

Fertility treatment

The evidence from a retrospective cohort study indicated that the risk of gestational hypertension/pre-eclampsia was higher among women who used assisted reproductive technology compared with the women who had not used it (adjusted OR 1.17, 95% CI 1.10–1.24)²¹ (see Risk factors evidence profile 1). A recent systematic review compared pregnancy complications of donor oocyte pregnancy with autologous oocyte in vitro fertilisation. It found that the risk of developing hypertensive disorders in pregnancy was significantly higher for donor oocyte pregnancy (OR 3.92, 95% CI 3.21–4.78).⁶⁹ Supporting this evidence, another concurrent systematic review found that the risk of pre-eclampsia is higher in oocyte-donation pregnancies compared with other methods of assisted reproductive technology (OR 2.54, 95% CI 1.98–3.24, $p < 0.0001$) or natural conception (OR 4.34, 95% CI 3.10–6.06, $p < 0.0001$)¹³ (see Risk factors evidence profile 2). Both reviews found that this increased risk was independent of maternal age or multiple gestation. Sperm donation also increased the risk of developing pre-eclampsia (OR 1.63, 95% CI 1.36–1.95).²⁰

Value of screening for maternal risk factors

While clinical guidelines recommend screening women for risk factors, evidence is lacking on how effective that strategy is when it treats each of the risk factors as separate screening tests, which produces additive detection and false positive rates.¹⁶ Evidence demonstrates that screening has potential clinical use only when it uses a combined algorithm that includes the various risk factors based on multivariate analysis.^{16,70}

Using algorithms based on logistic regression, a controlled cohort study (of 8,366 women) observed that predictors of early onset pre-eclampsia (<34 weeks) included: black ethnicity,* chronic hypertension, history of pre-eclampsia, and use of ovulation drugs. On the other hand, higher maternal age, BMI and family history or history of pre-eclampsia were predictors of late pre-eclampsia (34 weeks and after) and gestational hypertension.¹⁶ The estimated detection rates observed for early pre-eclampsia, late pre-eclampsia and gestational hypertension were 37% (95% CI 12.5–50.0), 28.9% (95% CI 21.2–37.6) and 20.7% (95% CI 14.3–28.4) respectively, at a 5% false positive rate¹⁶ (see Risk factors table 4).

Another multicentre cohort study of 3,529 nulliparous women (SCOPE study) demonstrated the value of using algorithms that combine multiple risk factors to predict pre-eclampsia.⁷⁰ Most women in this study were from New Zealand. The algorithm included risk factors (blood pressure, BMI and a family history of pre-eclampsia) along with less established factors, such as prolonged vaginal bleeding, low birthweight of the mother, and the woman's father having coronary artery disease. The evidence from this study indicated that the algorithm made predictions with moderate accuracy. The area under the receiving operating characteristics curve (AUC ROC) was 0.76, and detected 37% and 61% of women who developed pre-eclampsia, with a false positive rate of 10% and 25% respectively. Addition of

* This United Kingdom study asked women to identify their racial original from this list: White, Black, Indian or Pakistani, Chinese or Japanese and Mixed. From the context, we assume 'Black' is African or Afro-Caribbean.

information from ultrasonography did not significantly improve the performance of the algorithm, with an AUC ROC of 0.77.⁷⁰ The sensitivity and specificity of the risk score at 14–16 weeks in predicting pre-eclampsia were 27% (95% CI 22–34) and 95% (95% CI 94–96) respectively for a cut-off value of 5% false positives likelihood ratio (LR)+5.5 (4.2–7.2), LR–0.76 (0.70–0.84)⁷⁰ (Risk factors evidence profile 3). With a cut-off value of 10% false positives, the sensitivity and specificity were 37% (95% CI 30–44) and 90% (95% CI 89–91) LR+3.6 (2.9–4.5), LR–0.71 (0.63–0.79) respectively (Risk factors evidence profile 4) and with a cut-off value of 25% false positives; the sensitivity and specificity were 61% (95% CI 54–68) and 75% (95% CI 74–76) LR+2.5 (2.2–2.8), LR–0.52 (0.43–0.62)⁷⁰ (Risk factors evidence profile 5). The results of this study also demonstrated that negative prediction based on clinical risk assessment, with or without Doppler ultrasonography, was too inaccurate to allow a reduction in antenatal care.

The evidence reported here indicates that using algorithms to predict pre-eclampsia provides the first step towards a personalised risk prediction algorithm for pre-eclampsia. However, it is essential to gather further high-quality evidence and get external validation of the algorithms in other populations.

Evidence statement: Prediction – biomarkers and ultrasonographic markers

Predictive testing – recommendations

- Models for predicting pre-eclampsia, which combine different biochemical markers and uterine artery Doppler for all women, have shown mixed results. This guideline does not currently recommend using them. Although some show promise as potential screening tools, the evidence and experience of using them in clinical settings are not conclusive enough to include in this guideline.

Weak recommendation; very low-quality evidence

Introduction

Biomarkers: The explanations of the pathogenesis of pre-eclampsia suggest that endothelial dysfunction is associated with an imbalance of antigenic regulators and oxidative stress markers. This hypothesis has led to several research studies investigating possible biomarkers that could guide the diagnosis of pre-eclampsia. The biomarkers most commonly investigated are:

- **PlGF** (placental growth factor), a member of the vascular endothelial growth factor (VEGF) family of growth factors involved in regulating angiogenesis
- **s-Flt-1** (soluble fms-like tyrosine kinase 1), an enzyme that disables proteins that cause blood vessel growth
- **PAPP-A** (pregnancy associated plasma protein A), which is thought to be involved in local proliferative processes such as wound healing and bone remodelling
- **PP-13** (placenta protein-13),^{71,72,73,74} which generates various responses, such as immune responses, and influences other functions like apoptosis and molecular recognition
- hCG (human chorionic gonadotropin), a hormone the placenta produces during pregnancy.

Uterine artery flow: The trophoblast invasion of the spiral arteries, leading to mal-development of uteroplacental perfusion underlying the pathophysiology of pre-eclampsia, suggests that assessment of uterine artery flow has the potential to predict pre-eclampsia.^{75,76}

Biomarkers

The current evidence around biomarkers is of moderate to low quality. It is important to interpret it with caution and considering their usability in clinical practice.

A systematic review of 103 observational studies (432,621 women, singleton pregnancies at low risk in the first trimester) assessed the accuracy of serum biomarkers (PlGF, PP-13, PAPP-A and hCG) in predicting pre-eclampsia. Overall they had low predictive accuracy.⁷⁴ This review indicated that the best predictor was PlGF.

1. **PlGF** had cut-off values of LR+4.01 (95% CI 3.74–4.28) and LR–0.67 (95% CI 0.64–0.69), a pooled sensitivity of 0.56 (95% CI 0.52–0.61) and a pooled specificity of 0.91 (95% CI 0.89–0.92) (see Prediction evidence profile 1).⁷⁴
2. **PAPP-A** had a pooled sensitivity of 0.39 (95% CI 0.33–0.47) and a pooled specificity of 0.87 (95% CI 0.82–0.90) (see Prediction evidence profile 3).⁷⁴
3. **PP-13** had a pooled sensitivity of 0.47 (95% CI 0.39–0.54) and a pooled specificity of 0.89 (95% CI 0.85–0.91) (see Prediction evidence profile 5).⁷⁴

A systematic review of individual biomarkers also observed that PlGF is the most promising marker for predicting pre-eclampsia (sensitivity 0.65, 95% CI 0.63–0.67; specificity 0.89, 95% CI 0.89–0.89) compared with PAPP-A (sensitivity 0.30, 95% CI 0.29–0.32; specificity 0.92, 95% CI 0.92–0.92) and PP-13 (sensitivity 0.37, 95% CI 0.33–0.41; specificity 0.88, 95% CI 0.87–0.89) (see Prediction evidence profiles 2, 4, 6).⁷⁷

Other biomarkers such as **hCG**, **ADAM** and **Inhibin A** have been tested for their ability to predict pre-eclampsia (see Prediction evidence profiles 7, 8, 9). They all show poorer results than PlGF (see Prediction evidence profiles 1 and 2).^{74,77}

Evidence shows that the s-Flt-1:PlGF ratio is elevated in women with pre-eclampsia. Research with different cut-off levels has shown varying degrees of diagnostic accuracy.^{71,72,73} A case-control study⁷² (of 234 women with pre-eclampsia and a matched cohort consisting of 468 women with normal pregnancy outcome), using cut-offs for the s-Flt-1:PlGF ratio at ≥ 85 , showed varying results for different gestational ages.

- During early gestation (20–33 weeks), the s-Flt-1:PlGF ratio at ≥ 85 had a sensitivity of 88% and specificity of 99.5%.
- At gestation of more than 20 weeks, the sensitivity of the test was 76% and specificity was 95% (see Prediction evidence profile 10).
- At late gestation (≥ 34 weeks) s-Flt-1:PlGF ratio at ≥ 110 was 58%/95% respectively⁷² (see Prediction evidence profiles 11 and 12).

This study showed that a s-Flt-1:PlGF ratio of ≤ 33 was least likely to produce a negative test (0.05, 95% CI 0.02–0.13), whereas values ≥ 85 were most likely to produce a positive test (176, 95% CI 24.88–1,245). The evidence from the studies thus points to an approach with different cut-off levels of s-Flt-1:PlGF ratio based on the gestational phase in predicting pre-eclampsia.⁷²

Another study observed that s-Flt-1:PlGF ratio is also useful for predicting adverse outcomes in women at risk of pre-eclampsia (OR 9.5, 95% CI 6.1–15 with s-Flt-1:PlGF ratio >39.2) and in women at less than 34 weeks' gestation (OR 47.8, 95% CI 14.6–156.5)⁷¹ (Prediction evidence profile 14). A validation study using commercially available tests (550 women, 24–36 weeks' gestation) and a s-Flt-1:PlGF ratio of 38 or lower had a negative predictive value (ie, no pre-eclampsia in the subsequent week) of 99.3% (95% CI 97.9–99.9).⁷³ In this study, the positive predictive value of a s-Flt-1:PlGF ratio above 38 for a diagnosis of pre-eclampsia within four weeks was 36.7% (95% CI 28.4–45.7), with 66.2% sensitivity (95% CI 54.0–77.0) and 83.1% specificity (95% CI 79.4–86.3) (see Prediction evidence profile 13).

The advances in s-Flt-1:PlGF ratio assays hold promise for a predictive test of pre-eclampsia that is appropriate for clinical use. However, its clinical use is limited by the short duration of predictability of up to four weeks. Evidence from randomised controlled trials (RCTs) is needed to establish whether using this s-Flt-1:PlGF assay in clinical practice is more effective than the current standard of care in identifying those at risk of pre-eclampsia and bringing positive outcomes.

Ultrasonographic markers – uterine artery Doppler velocimetry abnormalities

A meta-analysis of 18 studies (of 55,974 women) evaluated the accuracy of first-trimester uterine artery Doppler velocimetry (UtADV) (between 11 and 14 weeks' gestation) to predict poor pregnancy outcomes, including pre-eclampsia and fetal growth restriction.⁷⁵ In predicting early-onset pre-eclampsia, abnormal uterine artery flow velocity waveform (FVW) had a sensitivity of 47.8% (95% CI 39.0–56.8) and a specificity of 92.1% (95% CI 88.6–94.6). In predicting early-onset fetal growth restriction, its sensitivity was 39.2% (95% CI 26.3–53.8) and its specificity was 93.1% (95% CI 90.6–95.0)⁷⁵ (see Prediction evidence profiles 15 and 16). Another cohort study (of 2,188 low-risk nulliparous women <21 weeks) demonstrated that second trimester UtADV has poor sensitivity for predicting

pre-eclampsia,⁷⁶ yet a meta-analysis of 74 studies of pre-eclampsia (total 79,547 women) demonstrated that UtADV provided a more accurate prediction of pre-eclampsia in the second trimester than in the first trimester and is dependent on the indices used.⁷⁸ This meta-analysis showed that most Doppler indices had poor predictive characteristics. One study of 351 women in this meta-analysis showed that an increased pulsatility index with notching had the best predictive accuracy of pre-eclampsia (LR+21.0, LR-82.0) among high-risk women in the second trimester with a sensitivity of 19% (95% CI 5–42) and a specificity of 99% (95% CI 97–100) (see Prediction evidence profile 17).

Although the evidence indicates UtADV is useful, it also highlights the need for predictive models using a combination of Doppler indices (uterine artery, cerebral and umbilical artery) that increase the predictive accuracy of UtADV in assessing the risk of pre-eclampsia.

Combination of biomarkers and UtADV

A systematic review of 37 observational studies among low-risk populations assessed the predictive performance of a combination of predictive tests.⁷⁹ The review demonstrated that biomarkers **PP13**, **PAPP-A**, **A disintegrin** and **metalloprotease-12 (ADAM12)**, **activin A** and **inhibin A**, measured in first or early second trimester and uterine artery Doppler in second trimester, have promising results (sensitivity 60–80%, specificity >80%) in predicting pre-eclampsia.

Other studies that have used fewer combinations show that the predictive performance for pre-eclampsia is low. A cohort study (of 1,104 women at 20–22 weeks' gestation) of a combination of abnormal UtADV and serum PlGF <188 pg/mL at 20–22 weeks showed it had a very poor association (OR 1.1, 95% CI 0.3–3.8; $p = 0.938$) with the occurrence of pre-eclampsia (sensitivity 61%, specificity 92%)⁸⁰ (Prediction evidence profile 18). Evidence from another cohort study assessed the predictability of UtADV with different PlGF cut-off levels (<280 pg/mL and >280 pg/mL) in women at 22–26 weeks' gestation. Women with abnormal UtADV and PlGF <280 pg/mL had a higher frequency of pre-eclampsia, early onset pre-eclampsia, severe pre-eclampsia, small for gestational age (SGA) without pre-eclampsia, placental abruption, eclampsia, and a composite of severe neonatal morbidity than both women with normal UtADV results and those with abnormal UtADV results and a PlGF ≥ 280 pg/mL (chi square for trend; $p < 0.001$).⁸¹ (See Prediction other evidence table.)

Comparisons with current practice

A cohort study of 3,529 low risk nulliparous women found that the best way of predicting preterm pre-eclampsia was to use a combination of PlGF, measured at 15 weeks, and a selection of easily attainable clinical risk variables: blood pressure, a family history of pre-eclampsia and a history of fertility treatment. The combination of uterine artery Doppler (20 weeks), PlGF (15 weeks) and endoglin (20 weeks) did not significantly improve prediction over either the combination of PlGF or the clinical risk variables alone. The predictability of PlGF alone (22%, 95% CI 12–35) for the development of pre-eclampsia was less than that of clinical risk factors (34%, 95% CI 31–59).⁸²

Other factors: Clinical use, cost-effectiveness and the woman's preferences

- The evidence highlights the limitations of the available prediction tests for clinical use. In particular, it shows that the predictability has only a short duration and that cut-off points differ, making it impractical to use such tests in clinical settings.
- No RCTs provide evidence on whether using predictive tests in clinical practice could improve maternal and fetal adverse outcomes or produce similar results to the current standard of care.
- No evidence is available on the cost-effectiveness of these tests. One study in the United Kingdom noted that using UtADV in addition to the current practice of a first trimester scan would cost an

additional £18–25.⁷⁵ Although the false-positive rate is low for UtADV, the low sensitivity is likely to add to the anxiety of the women as well as clinicians.

- Predictive tests also have harms. Any test with false positives can cause anxiety (and false negatives can cause false reassurance). If doctors act on a predictive test for pre-eclampsia inappropriately (eg, by considering it to be a diagnostic test), there is the real potential to cause substantial morbidity through iatrogenic premature birth of an infant. It is essential that a novel biomarker test has adequate test performance to minimise such harms, and that the implications of a positive result for consequent management are also considered.
- Experiences related to education and women’s choices need to be considered when deciding whether to support the possible use of predictive tests.

Evidence statement:

Women's experience and engagement

Women's experience – recommendations

- Make educational tools available to help women understand issues relating to hypertension in pregnancy and pre-eclampsia. Such tools should take into consideration women's different levels of health literacy and demographic diversity.
Strong recommendation; very low-quality evidence
- Work is needed to ensure equity of care for all women, in particular, Māori and Pacific women who are over-represented in poor obstetric outcomes.
Strong recommendation; very low-quality evidence
- It is a priority to give women the opportunity to discuss their options for management of care with practitioners with clinical experience and knowledge of current research about hypertensive disorders in pregnancy.
Strong recommendation; very low-quality evidence
- Complications associated with hypertensive disorders in pregnancy can be very stressful. Assess, address and document women's need for psychological care and support (eg, community organisations, mental health services and cultural support), both antenatally and postpartum.
Strong recommendation; very low-quality evidence
- Actively involve women and their families and whānau and keep them informed throughout the health decision-making process.
Strong recommendation; very low-quality evidence
- Normal screening for postnatal depression is imperative. A woman may need additional support because she is more likely to have post-traumatic stress disorder and depression after experiencing severe hypertension or pre-eclampsia in pregnancy.
Strong recommendation; very low-quality evidence
- Give women the opportunity to debrief after experiencing hypertension or pre-eclampsia in pregnancy. Discuss what this means for future pregnancies and their long-term health.
Strong recommendation; very low-quality evidence

Introduction

A range of activities can help to build understanding of women's experiences by capturing direct feedback from women, service users, carers and wider communities. Along with information on clinical outcomes and other intelligence, this knowledge can inform how to improve quality and reshape services. Another strong focus is on engaging women in decisions about their own care, as well as how to run services and, increasingly, prioritise services. Because New Zealand studies of women's experience of pre-eclampsia and hypertension in pregnancy are rare the evidence presented below mainly comes from international research. Note that these findings may have limited relevance to New Zealand and may not easily translate to this context because New Zealand's health care and maternity system and its ethnic mix are unique.

Knowledge

The experience of pregnancy is often laced with anxiety for women with pre-eclampsia. Research has demonstrated that women with hypertensive disorders in pregnancy have a generally poor understanding of signs and symptoms of pre-eclampsia, which may explain why they do not seek timely care. An Australian study (of 112 members of the consumer group) indicated that most women

(77%) had no knowledge of pre-eclampsia before they were diagnosed with it and, once diagnosed, half (50%) did not appreciate how serious or life threatening it was.⁸³ On the other hand, a qualitative study has shown that women with an increased risk of pre-eclampsia would be willing to engage in efforts to reduce that risk.⁸⁴ However, the study also found that the women identified as at risk of pre-eclampsia fell into two different groups in terms of their coping strategies. The first group, who had an internal sense of control, focused on the risk that pre-eclampsia presented to them and coped by seeking information, making positive behaviour changes and adjusting the way they looked at their situation (cognitive reappraisal). The second group, who had an external sense of control, focused on the risk that pre-eclampsia presented to the fetus and coped by using avoidance strategies.⁸⁴ This study also observed that, despite having different coping strategies, women with high risk appeared to be generally receptive to the increased monitoring.

In the Australian study described above, women's experience made them substantially more anxious about future pregnancies and partners; friends and relatives similarly expressed fear for the woman and/or her baby and had no prior understanding of pre-eclampsia.⁸³ Women wanted access to information about pre-eclampsia as their pre-eclampsia experience had a substantial effect on them, their confidants and their babies, as well as on their approach to future pregnancies.⁸³

A study in the United States of America explored the extent to which pregnant women understand the symptoms and potential complications of pre-eclampsia. It demonstrated that women were able to correctly answer only 43% of the questions assessing pre-eclampsia knowledge and only 14% of the women were able to provide a definition that correctly reflected the syndrome.⁸⁵ The USA study observed that women tended to get more correct answers to the questionnaire if they had higher literacy, multiparity and a history of pre-eclampsia, and had received information about pre-eclampsia from a clinician or another information source (eg, the internet, television, a book or a friend).⁸⁵

A Brazilian study used a word-association test to explore perceptions of pre-eclampsia. The words pregnant and postpartum women tended to associate with pre-eclampsia were fear, risk, care and lack of information, while health professionals related it more to aspects of care. The findings suggest a gap in the experiences of pre-eclampsia.⁸⁶

Pre-eclampsia and mental health

A link between depression and pre-eclampsia before pregnancy

Current evidence suggests hypertension in pregnancy is linked to maternal depression and anxiety. A recent observational study (of 1,317 women at 16–27 weeks' gestation) suggested that the link between maternal chronic hypertension and depression/anxiety symptoms occurs before pregnancy.⁸⁷ In addition, the researchers observed that chronic hypertension was the main driver behind these associations (adjusted OR = 2.7–3.5). Pre-eclampsia accompanied by preterm birth was also linked to women's lifetime history of depression symptoms (OR 2.3; 95% CI 1.0–5.2).⁸⁷

Postpartum mental health

Other studies have shown post-traumatic stress disorder (PTSD) after birth is linked with women who had pre-eclampsia or HELLP.^{88,89,90} A longitudinal evaluation (of 175 women) showed that at six weeks after childbirth, the prevalence of PTSD, but not depression, was significantly higher in these women than in a control group (14% vs 3%, $p = 0.023$). Having a history of depression or depressive symptoms during pregnancy and infant death was significantly associated with symptoms of postpartum PTSD. At 15 months postpartum, 11% of women with pre-eclampsia had PTSD, some of whom had not had PTSD at six weeks postpartum.⁸⁸ Another study (of 149 women) showed that the prevalence of PTSD was 8.6% at six weeks and 5.1% at 12 weeks postpartum.⁸⁹ Among three case studies reported in another article, a Dutch survey of 115 women who experienced HELLP syndrome found 24% showed signs of PTSD and 31% refused to consider future pregnancies out of fear.⁹⁰

Another finding is that women who experience pre-eclampsia have a lower health-related quality of life after giving birth. A cohort study (of 174 women) showed that those who had a severe pre-eclampsia had lower quality of life at six weeks postpartum than those who had mild pre-eclampsia (all $p < 0.05$) but improved on almost all the health scales from 6–12 weeks postpartum ($p < 0.05$).⁸⁹ In this study, women who had mild pre-eclampsia, compared with those who experienced severe pre-eclampsia, had a poorer emotional quality of life at 12 weeks postpartum ($p < 0.05$). The experiences of admission to the neonatal intensive care unit and perinatal death were identified as the factors contributing to this poorer quality of life.⁸⁹

These studies indicate that women who have pre-eclampsia and its complications should receive appropriate postpartum psychological care and behavioural interventions.^{88,89} Researchers have suggested that contact with other women who have had severe disease could be potentially effective as a behavioural therapy intervention.⁹⁰ According to one systematic review of 14 studies on midwifery interventions to reduce PTSD following childbirth, the evidence is insufficient to support the recommendation of any midwife-led intervention to address postpartum PTSD.⁹¹ Another important consideration is how the condition and the pregnancy event in general affect the woman's family and whānau.⁹²

Education

Education for maternity caregivers

A systematic review of implementing clinical guidelines in obstetrics demonstrated that:

- educational strategies with medical providers were generally ineffective
- educational strategies with paramedical providers and opinion leaders, qualitative improvement, and academic detailing have mixed effects
- audit and feedback, reminders and multifaceted strategies are generally effective.⁹³

Other researchers have observed that health care providers are often under-informed. For example, in a USA study obstetricians and gynaecologists showed great disparities in their knowledge and management of hypertensive disorders in pregnancy.⁹⁴ As a first step in educating women and providing the best care, health care providers need to be more uniform in their knowledge and approach to hypertensive disorders in pregnancy. Research also indicates that overcoming traditionally unequal clinician–woman power relationships so that they work in partnership improves communication around high-risk pregnancies.⁹⁵

Education for women

A systematic review of 13 peer-reviewed qualitative studies on antenatal education examined women's views and experiences. It demonstrated that women prefer a small-group learning environment in which they can talk to each other as well as the educator and can relate information to their individual circumstances.⁹⁶ In addition, researchers observed that pregnant women enjoy learning from each other and respect and value the input of other women who have recently been through the experiences they are about to face themselves.⁹⁶ This indicates support groups and networks have a highly valuable role for women currently experiencing hypertensive issues or who have been through the experience themselves.

These studies also emphasise the need for midwives and obstetricians to actively participate in educating women about self-monitoring of fetal activity and maternal symptoms (eg, headaches, blurred vision, and epigastric pain). Furthermore, keeping women informed on the rationale behind the tests (eg, laboratory analysis, non-stress test) and treatments (eg, magnesium sulphate, antihypertensive) specific to the individual may help to alleviate stress and anxiety during an emotionally and physically trying time.⁹⁷

Another barrier to education is the limited time in one-to-one consultation where many important issues need to be addressed, often resulting in information overload.⁹⁶ However, this finding is linked to the pregnancy care model in the local settings of the study. In New Zealand, the continuity of care model should offer better opportunities for education on hypertensive disorders in pregnancy,⁹⁸ but this idea needs to be further explored.

Health literacy

Other studies have observed that many educational materials for women, such as pamphlets, require a level of literacy that is too high for general public understanding.^{99,100} An RCT that compared the effectiveness of different educational tools indicated that a standardised graphic-based educational tool produced better knowledge of pre-eclampsia than a general information pamphlet or no additional information (71%, 63%, 49% respectively, $p < 0.05$). This finding applied equally among women with and without adequate health literacy.⁸⁵

One suggestion is that writing more clearly is a simple way of adjusting current educational material (on websites or pamphlets), which may increase comprehension regardless of the reader's level of health literacy. Using pictures and videos may also be an effective way of increasing a woman's comprehension of health information that is too complex to fully explain through text alone.¹⁰⁰ These suggestions raise important issues related to health literacy and adult education and indicate that it is important to follow local experiences and guidelines on health education. Specifically for New Zealand, *Rauemi Atawhai* will prove to be a useful guide in developing education tools.¹⁰¹

Patient rights and decision-making

The health care system and health professionals have the ethical responsibility to provide adequate information using culturally sensitive approaches to ensure women understand the implications and complications of hypertensive disorders in pregnancy. Related to this is the importance of ensuring continuity of care in referral to secondary services, which requires a three-way discussion about ongoing care and clinical responsibility between the LMC, the specialist and the woman.¹⁰² In line with the Health and Disability Commissioner Act 1994 and the associated patient code, such discussions should acknowledge and explain the woman's rights.¹⁰³

This guideline also acknowledges the principles of partnership, protection and participation as an affirmation of the Treaty of Waitangi and the health system's responsibilities towards Māori as tangata whenua of Aotearoa New Zealand. Education must adopt these principles – an approach that is also known to improve women's experiences.

It is vital that, throughout the experience, health professionals fully inform women and their families and whānau and advise them of their options for care so that they are able to give fully informed consent. One study found that, although most women want to be actively involved in health decision-making during a high-risk pregnancy, some prefer a passive role. In achieving active involvement, the setting of antenatal care was less important than the ability of carers to support the woman in decision-making.¹⁰⁴

Location of care

Women with hypertensive disorders may need to receive care remote from their family, friends and usual support networks. This will often create additional stress for them.^{105, 106, 107} Health professionals should make social services available, offer contacts with support groups and give them access to any travel and accommodation assistance they are eligible for through health systems.

Demographic effects

Another important aspect of women's experience is the socioeconomic implications of different interventions and advice. A study in South Auckland (of 826 women of Māori, Asian, European and other ethnicities) showed that 17% booked for antenatal care at later than 18 weeks' gestation ('late bookers').¹⁰⁸ The results demonstrated that women were significantly more likely to book late for antenatal care if they had limited resources (OR 1.86, 95% CI 1.17–2.93), had no tertiary education (OR 1.96, 95% CI 1.23–3.15) or were not living with a husband/partner (OR 2.34, 95% CI 1.48–3.71). In addition, the odds of late booking for antenatal care were almost six times higher among Māori women (OR 5.70, 95% CI 2.57–12.64) and Pacific women (OR 5.90, 95% CI 2.83–12.29) compared with those of European and other ethnicities.¹⁰⁸

The findings from the 'Growing up in New Zealand' study demonstrated that whether women engaged an LMC provider, and whether they had a choice of provider, varied depending on their demographics.¹⁰⁹ Women who did not engage an LMC were more likely to be non-European, under 20 years or over 40 years old, with poorer educational attainment or living in more deprived households. Women who did not have a choice of provider were more likely to be non-European, under 20 years old or living in more deprived households.¹⁰⁹ These findings give further support to the call for more focused engagement of the maternity care providers with pregnant women of non-European ethnicities and deprived households to improve antenatal care and support women in following specific advice in relation to hypertension in pregnancy.

Evidence statement: Lifestyle (diet, physical activity, supplements)

Lifestyle – recommendations

- Excessive weight gain in pregnancy puts women at risk of developing hypertensive disorders. This risk is even greater in women who are obese when they become pregnant. An optimal gestational weight gain for these women is 5–9 kg. Give specific education around optimal gestational weight gain.
Weak recommendation; very low-quality evidence
- Give routine advice on healthy eating, smoking cessation, alcohol intake and mild to moderate exercise to all women in the antenatal period, as well as weighing them regularly. Further randomised control trials are needed to determine the effects of these interventions on hypertensive disorders in pregnancy.
Strong recommendation; low-quality evidence
- Folic acid and iodine supplements are recommended in all pregnancies to reduce the risk of spina bifida and promote normal brain development. However, no conclusive evidence is available to indicate that these supplements reduce the risk of developing HDP or pre-eclampsia.
Weak recommendation; low-quality evidence
- Currently there is no strong evidence to show that multi-vitamins or other supplements such as fish oil and magnesium reduce the risk of developing HDP or pre-eclampsia.
Strong recommendation; moderate-quality evidence
- This guideline does not recommend vitamin C and vitamin E supplementation. Such supplementation may cause harm because high levels (eg, vitamin C 1,000 mg and vitamin E 400 IU) are linked with an increased risk of low birthweight babies.
Strong recommendation; moderate-quality evidence
- This guideline does not recommend salt restriction in women at risk of pre-eclampsia.
Strong recommendation; moderate-quality evidence
- This guideline does not recommend bed rest and restriction of physical activity in women at risk of pre-eclampsia.
Strong recommendation; very low-quality evidence

Introduction

In women who are not pregnant, treatment of hypertension usually focuses on two basic strategies:

1. lowering blood pressure
2. minimising additional cardiovascular risk factors.

This evidence statement will look at the evidence of these interventions as well as vitamin/antioxidant supplementation in the context of reducing the risk of developing pre-eclampsia in pregnant women with hypertension.

Dietary salt restriction

The evidence on effectiveness of salt restriction is based mainly on the Cochrane systematic review of two trials involving 603 women.¹¹⁰ These trials found salt restriction did not significantly reduce risk of pre-eclampsia (RR 1.11, 95% CI 0.46–2.66) (see Lifestyle evidence profile 1). However, the wide confidence interval of these findings means that the true effect could be anywhere from more than

halving to more than doubling the risk of pre-eclampsia associated with salt restriction. The trials were relatively small and therefore may be unable to detect benefit. Larger trials are needed to confirm their results.

Antioxidants, vitamins and supplements

The hypothesis that antioxidants can reduce the risk of pre-eclampsia was linked to the oxidative stress suggested in the pathogenesis of pre-eclampsia. The evidence comes from a Cochrane review of 10 trials involving 6,533 women¹¹¹ and a systematic review of 19,810 women.¹¹² The evidence did not demonstrate antioxidants (vitamin C and/or vitamin E) significantly reduced the risk of pre-eclampsia (RR 0.73, 95% CI 0.51–1.06) (see Lifestyle evidence profiles 2 and 3). In addition, evidence from five trials in this Cochrane review did not show benefit for reducing risk of preterm birth before 37 weeks (RR 1.10, 95% CI 0.99–1.22) or small for gestational age babies (RR 0.83, 95% CI 0.62–1.11). Women supplemented with vitamin C and E were at increased risk of premature rupture of the membranes (RR 1.73, 95% CI 1.34–2.23) (see Lifestyle evidence profile 2). However, a study comparing vitamin C alone and placebo found those taking the supplement had a decreased chance of preterm premature rupture of membranes (PPROM) (RR 0.66, 95% CI 0.48–0.91) (see Lifestyle evidence profile 3).

Other RCTs not included in the Cochrane review show similar findings, with no significant benefit for maternal or fetal outcomes for those women given vitamin C and E supplements compared with those given a placebo.^{113,114} One large RCT (the VIP trial) showed possible harm of these supplements, associating them with low birthweight babies.¹¹⁵ The daily doses of vitamin C and vitamin E that were administered in this study (vitamin C 1,000 mg and vitamin E 400 IU) were below the maximum recommended intake in pregnant women.

Another suggestion is for vitamin D supplementation based on studies indicating a correlation between low vitamin D levels and pre-eclampsia.¹¹⁶ However, the evidence is inadequate to draw reliable conclusions on the role of supplementation in preventing hypertensive disorders in pregnancy. The available evidence is from one RCT of 400 women that combined vitamin D with calcium supplements.¹¹⁷ This trial showed no significant benefit (RR 0.67, 95% CI 0.33–1.35) in preventing pre-eclampsia (see Lifestyle evidence profile 4). Another systematic review of both observational and randomised studies suggests that vitamin D supplementation alone earlier in pregnancy may help reduce the risk of pre-eclampsia: two observational studies had a pooled OR of 0.81 (95% CI 0.75–0.87) and four randomised studies had a pooled OR of 0.66 (95% CI 0.52–0.83)¹¹⁸ (see Lifestyle evidence profile 5). The findings of this review¹¹⁸ also suggested an association between higher serum 25(OH)-D levels and a reduced risk of pre-eclampsia but they were not conclusive as it was not possible to rule out that the reduced risk caused the higher serum levels, rather than vice versa.

The evidence of the effect of fish oil/omega-3 in reducing the risk of pre-eclampsia comes from one RCT of 400 women. That study showed this supplement had a significant benefit in preventing pre-eclampsia (RR 0.09, 95% CI 0.01–0.73)¹¹⁹ (see Lifestyle evidence profile 6). However, the evidence is of very low quality and insufficient to draw reliable conclusions about fish oil/omega-3 for clinical practice. Larger RCTs are needed for more conclusive evidence.

While folic acid is a routine supplement in pregnancy for protection against spina bifida, several studies suggest this supplement may reduce also the risk of pre-eclampsia. Research shows folate biomarkers are low in women with pre-eclampsia.¹²⁰ However, pooled results of 11 studies and 1,276,063 women indicate that folic acid fortification alone was not associated with the occurrence of gestational hypertension (RR 1.03, 95% CI 0.98–1.09, $p = 0.267$) and pre-eclampsia (RR 0.99, 95% CI 0.90–1.08, $p = 0.738$). However, the evidence suggests supplementation of pregnancy-specific multivitamins containing folic acid could prevent gestational hypertension (RR 0.57, 95% CI 0.43–0.76, $p < 0.001$) and pre-eclampsia (RR 0.64, 95% CI 0.48–0.84, $p = 0.001$)¹²¹ (see Lifestyle evidence profile 7).

This evidence statement does not cover iodine and magnesium supplementation because only two few studies are available and these are of very low quality.^{122,123}

Physical activity and rest

The evidence on the benefit of restricted or unrestricted physical activity is inadequate at present. It comes primarily from a Cochrane systematic review of two trials, involving 106 women in total which compared the effects of rest or restricted activity with unrestricted or normal activity. One trial (32 women) demonstrated that rest reduced the risk of pre-eclampsia compared with unrestricted activity (RR 0.05, 95% CI 0.00–0.83)¹²⁴ (see Lifestyle evidence profile 8). However, the Cochrane review authors note that the reported effect may reflect bias and/or random error rather than being a true effect.

Reviews of observational studies have shown physical activity in early pregnancy can reduce the risk of pre-eclampsia (RR 0.79, 95% CI 0.7–0.91), with walking showing particular benefit (RR 0.68, 95% CI 0.51–0.89)¹²⁵ (see Lifestyle evidence profile 9). Researchers have suggested that physical activity stimulates placental angiogenesis and may have a role in reversing maternal endothelial dysfunction.^{126,127} Large RCTs are needed to gather reliable evidence on the effect of physical activity on reducing the risk of hypertension in pregnancy.

Gestational weight gain

While beginning a pregnancy with a high BMI is a risk for hypertensive disorders, targeted weight gain during pregnancy is associated with improved outcomes for both the mother and the baby regardless of the mother's existing weight. However, an estimated one-third of women of normal weight and 60% of obese women gain more than the recommended weight during pregnancy. A Dutch prospective population cohort study (of 6,956 pregnant women) found that excessive weight gain, compared with low or recommended weight gain, was associated with a higher risk of gestational hypertension (OR 2.07, 95% CI 1.43–2.99). It also found that, compared with mothers of normal weight, those who were overweight had increased risks of gestational hypertension (OR 2.15, 95% CI 1.55–2.97) and pre-eclampsia (OR 1.91, 95% CI 1.21–3.00)¹²⁸ (see Lifestyle other evidence table).

A 2014 meta-analysis¹²⁹ that included 23 RCTs (4,990 women) found that increased gestational weight gain was associated with an increase in the incidence of pre-eclampsia (0.2% per gained kilogram, 95% CI 0.5–0.9), although that increase was not statistically significant. It also investigated interventions to ensure healthy weight gain (exercise and dietary advice). The interventions had no significant effect on the incidence of pre-eclampsia compared with the controls (see Lifestyle other evidence table).

Another large retrospective population study of nulliparous women found that women with excessive weight gain (in relation to Institute of Medicine guidelines⁶⁵), particularly those who gained 9 kg or more, were more likely to have adverse maternal outcomes (pre-eclampsia: AOR 2.78, 95% CI 2.82–2.93; eclampsia: AOR 2.51, 95% CI, 2.27–2.78).⁶⁶

High-sugar diets are also associated with increased risk of pre-eclampsia whereas high fruit and vegetable diets are linked with a decreased risk.^{130,131} One systematic review analysed interventions to restrict gestational weight gain and their effect on obstetric outcomes. It found interventions were associated with a reduced risk of pre-eclampsia (0.74, 95%CI; 0.60–0.92).¹³²

For guidance and resources around gestational weight gain for women and clinicians, see the Ministry of Health's *Guidance for Healthy Weight Gain in Pregnancy*.¹³³ That guidance recommends routine antenatal weighing. A recent pilot RCT showed this approach was acceptable to women and reduced excessive weight gain¹³⁴ (see Lifestyle other evidence table).

Other factors

While recognising the limitations in current evidence, this guideline recommends that health professionals consider the woman's preferences when they are advising on lifestyle and dietary interventions. Some women may not want to modify their diet or physical activity patterns either because they prefer not to or because of their social and financial circumstances. However, when pregnant women have a healthy diet and moderate exercise, lifestyle factors which lead to appropriate gestational weight gain, it improves many maternal and neonatal outcomes.¹³³

Evidence statement: Aspirin prophylaxis

Aspirin prophylaxis – recommendations

- Aspirin (100 mg daily) is indicated in women at high risk of developing pre-eclampsia. They should begin taking it before 16 weeks' gestation. Evidence on the efficacy and safety of starting low-dose aspirin before 12 weeks' gestation is currently limited.
Strong recommendation; moderate-quality evidence
- Women can remain on aspirin until they give birth.
Weak recommendation; very low-quality evidence

Introduction

The evidence profile shows that low-dose aspirin (50–150 mg) has a modest protective effect in reducing adverse outcomes in women at high risk of pre-eclampsia. Researchers have suggested that a systemic prostaglandin-thromboxane imbalance and an excessive inflammatory response are involved in the pathophysiology of pre-eclampsia, and that aspirin has a protective effect as an anti-inflammatory agent blocking key cytokines and the production of thromboxane, a stimulant of platelet aggregation.^{135,136}

Overall effect

The evidence on the effectiveness of low-dose aspirin is based mainly on the Cochrane systematic review of 46 trials involving 32,891 women.¹³⁷ In this review, using antiplatelet agents, specifically low-dose aspirin prophylaxis, reduced the risk of pre-eclampsia by 17% (RR 0.82, 95% CI 0.76–0.89) (see Aspirin evidence profile 1). Furthermore, this approach reduced preterm births by 8%, SGA babies by 10% and perinatal deaths by 14%. The review observed no significant differences for other important outcomes for those treated with aspirin compared with the control group.

Another systematic review of six RCTs (of 898 women with multiple gestations) also observed a significant reduction in the risk of pre-eclampsia (RR 0.67, 95% CI 0.48–0.94) and mild pre-eclampsia (RR 0.44, 95% CI 0.24–0.82) with low-dose aspirin. However, it found no such reduction in severe pre-eclampsia (RR 1.02, 95% CI 0.61–1.72)¹³⁸ (see Aspirin other evidence table).

Effect of risk prevalence

Although the evidence demonstrated that the difference based on maternal risk* is not statistically significant, there is an absolute risk reduction for those at high risk (a risk reduction of 5% in high risk women compared with 0.8% in moderate risk women) (see Aspirin evidence profile 1).¹³⁷

In applying this evidence, it is important to note that the NNT is determined by the effect size and the prevalence of the clinical condition. The evidence from the PARIS collaborative group's meta-analysis of individual patient data from 63 studies of 38,026 women demonstrated that for those at low risk (2% baseline event rate), it would be necessary to treat 500 women (RR 0.9; 95% CI 0.84–0.97) while for high-risk women (18% baseline event rate) the NNT would be 56 to prevent one case of pre-eclampsia¹³⁹ (see Aspirin evidence profile 2).

* This Cochrane systematic review defined high risk as having one or more of the following: previous severe pre-eclampsia, diabetes or chronic hypertension. It defined moderate risk as having any other risk factors, in particular: first pregnancy, a mild rise in blood pressure and no proteinuria, abnormal uterine artery Doppler scan, positive roll-over test, multiple pregnancies, a family history of severe pre-eclampsia and being a teenager, having renal disease or autoimmune disease.

A chronological cumulative meta-analysis of published systematic reviews on the effect of low dose aspirin on pre-eclampsia has suggested possible bias against null hypothesis and the need for additional studies¹⁴⁰ (see Aspirin other evidence table).

Effect of timing

Gestation when starting treatment

The Cochrane systematic review demonstrated no significant difference in reducing the risk of pre-eclampsia between those who started low-dose aspirin at 20 weeks' gestation or earlier and those who started it after 20 weeks.¹³⁷ However, a more recent meta-analysis of 34 RCTs of 11,348 women demonstrated that the risk of pre-eclampsia and eclampsia decreases significantly among women who began low-dose aspirin between 12 and 16 weeks' gestation compared with those started after 16 weeks¹⁴¹ (see Aspirin evidence profile 4).

Two other meta-analyses of RCTs (one with three studies of 346 women¹⁴² and another with four studies of 392 women¹⁴³) had similar findings (see Aspirin evidence profiles 5 and 6). Other studies have shown that starting aspirin before 17 weeks reduced the risk for late-onset pre-eclampsia by 29%, supporting the practice of starting aspirin early in high-risk women¹⁴⁴ (see Aspirin other evidence table). In the trials reported in the systematic reviews and meta-analyses, the earliest gestation at which women began taking low-dose aspirin was 12 weeks. The evidence for the effectiveness of starting aspirin prophylaxis in the first trimester (before 12 weeks) is lacking for outcomes related to hypertensive disorders in pregnancy.

Time of day

Evidence shows that the time when women take aspirin affects the outcomes. A prospective, randomised, double-blind, placebo-controlled, chronotherapy trial assigned 350 high-risk pregnant women at 13.5 ± 1.4 weeks of gestation to one of six groups, defined according to treatment (placebo or aspirin 100 mg/day) and time of treatment: when they woke up, eight hours after they woke up or at bedtime/evening. It showed that the effects of aspirin on ambulatory blood pressure depended strongly on administration time.¹⁴⁵ This study demonstrated that, compared with placebo, taking aspirin when waking up had no effect on blood pressure, but taking it eight hours after waking up and, even more so, taking at bedtime had a highly significant effect ($p < 0.001$).

Further analysis combined those who took aspirin when they woke up and those who took it eight hours after waking up into one group and then compared that group to those who took it at bedtime. The results showed the combined (morning and eight hours) group had a greater event rate of serious adverse outcomes, which was highly statistically significant (RR 0.19, 95% CI 0.10–0.39; $p < 0.001$).¹⁴⁵ Other studies have had similar results.¹⁴⁶ However, a recent systematic review on the topic suggests more research is needed in this area¹⁴⁷ (see Aspirin other evidence table).

When to stop treatment

The time when women stop aspirin prophylaxis varies. In a review of 21 RCTs, five studies explicitly stated the final date (ie, 2 weeks or 10 days before the estimated date of birth, 34 completed gestational weeks or 38 gestational weeks). Two studies did not clearly specify an end point. In the remaining 13 studies, the women continued using aspirin until they gave birth. Stopping aspirin according to a plan as compared with continuing to take it to birth seemed to have no effect on poor outcomes.¹⁴⁸

Effect of dose

The Cochrane systematic review and the PARIS collaborative group's meta-analysis of individual data demonstrated that the risk reduction effect of low-dose aspirin (50–150 mg/day) on maternal and fetal

outcomes (including adverse effects: placental abruption, antepartum and postpartum bleeding) was consistent across different doses.^{137,138} The evidence demonstrated no significant difference in risk reduction or adverse effects with doses of 75 mg or less (50–75 mg/day) and doses more than 75 mg (80–150 mg/day) (see Aspirin evidence profile 3).

In a further subgroup analysis of doses 60 mg, 75 mg, 100 mg and 150 mg per day, the NICE guideline development group demonstrated the dose level did not significantly reduce risk except in the 75 mg per day subgroup (60 mg subgroup: 14 studies, RR 0.92, 95% CI 0.84–1.00; 100 mg subgroup: 13 studies, RR 0.71, 95% CI 0.50–1.02; 150 mg subgroup: 3 studies, RR 0.95, 95% CI 0.67–1.35).³³ However, the reviewers acknowledge that this analysis may have been underpowered to detect a difference because it involved only a few studies.

Adverse effects and safety

As with any medication, health professionals should take care with prescribing aspirin because of its interactions with other drugs and pre-existing conditions. The list below covers some of these precautions but it is not exhaustive.

Be cautious when giving aspirin to women:

- with asthma (up to 20% of asthmatics may be affected).¹⁴⁹ One study in a systematic review¹⁵⁰ found that half of those who reacted did so at low doses of aspirin (≥ 80 mg)
- having anticoagulant treatment (eg, thromboembolic prophylaxis)
- with previous peptic ulceration (low-dose aspirin is not contraindicated but should be used with caution)
- already using proton pump inhibitors or histamine H₂-receptor antagonists.¹⁵¹

Gastric side effects of aspirin are usually associated with long-term use (ie, longer than a normal pregnancy) and in higher doses. However, health professionals should monitor signs of gastritis or gastric ulceration. They should also advise all pregnant women not to take additional aspirin as a pain reliever.

The Cochrane systematic review demonstrated that low-dose aspirin is safe with no major adverse effects such as abruption of placenta when women start it between 12 and 16 weeks of gestation¹³⁷ (see Aspirin evidence profiles 1 and 3). Two studies in this review reported on adverse effects on the infant at 12–18 months and found no effects. The other reported a higher risk of motor problems (fine or gross), but the quality of this study was low due to problems of allocation concealment and loss to follow-up (see Aspirin evidence profile 1).

The PARIS collaborative group study confirmed that taking low-dose aspirin is safe by demonstrating no significant effect on antepartum or postpartum haemorrhage and infant bleeding when women started taking it late in the first trimester.¹³⁸ Evidence for the safety of low-dose aspirin in the first trimester comes from a Cochrane systematic review examining effects on miscarriages.¹⁵² In this review, one RCT on adverse outcomes demonstrated no significantly higher risk of congenital malformations or bleeding with aspirin prophylaxis (see Aspirin evidence profile 7). This evidence is consistent with findings from an earlier meta-analysis of eight (case control and cohort) studies that observed no increased risk of overall congenital malformations (OR 1.33, 95% CI 0.94–1.89) or cardiac malformation (OR 1.01, 95% CI 0.91–1.12) in infants whose mothers took low-dose aspirin in the first trimester.¹⁵³ However, a subgroup analysis of five studies in this meta-analysis observed an increased risk of gastroschisis among those with aspirin prophylaxis (OR 2.37, 95% CI 1.44–3.88), independent of pre-eclampsia^{151,154} (see Aspirin other evidence table). The absolute risk of gastroschisis in the general population is 5.16 per 10,000 live births.¹⁵⁵

Most studies did not specify the dose of aspirin women took, so the GDT could not analyse outcomes based on dose. The risks of low-dose aspirin in the first trimester are currently unknown.

Other factors

The cost-effectiveness of low-dose aspirin is indisputable for women at risk of pre-eclampsia. Cost-benefit analyses in the United Kingdom showed that low-dose aspirin generates 0.52 extra quality-adjusted life years over the length of pregnancy.¹⁴¹ Simulations of different models in the USA showed that a universal prophylaxis with aspirin was the most cost-effective approach.¹⁵⁶ Sixty-eight women (NNT) with two or more moderate risk factors would need low-dose aspirin prophylaxis to prevent one case of pre-eclampsia, 56 women to prevent one preterm birth and five women to prevent one maternal death.^{148,152}

One further factor to consider is that aspirin 100 mg is already fully subsidised in New Zealand. However, some women may prefer the practical ease of buying low-dose aspirin (which is also quite cheap) from the supermarket.

Evidence statement: Calcium supplementation

Calcium supplementation - recommendations

- For women at high risk of pre-eclampsia, offer calcium supplementation along with dietary advice to achieve 1 g elemental intake per day, from booking to birth.
Strong recommendation; moderate-quality evidence

Introduction

Low calcium intake may cause high blood pressure by stimulating either parathyroid hormone or renin release, and in that way increasing intracellular calcium in vascular smooth muscle leading to vasoconstriction. A possible mode of action for calcium supplementation is that it reduces parathyroid release and intracellular calcium and so reduces smooth muscle contractility. By a similar mechanism, calcium supplementation could also reduce uterine smooth muscle contractility and prevent preterm labour and birth. Calcium may also have an indirect effect on smooth muscle function by increasing magnesium levels.^{157,158,159,160}

Overall effect

The evidence showing calcium supplementation can reduce the risk of hypertensive disorders comes mainly from a Cochrane systematic review¹⁵⁸ of:

1. 13 randomised controlled trials involving 15,730 women that studied the effect of taking more than 1 g per day
2. 10 quasi-random trials of 2,234 women on the effect of taking less than 1 g per day in supplements.

This Cochrane review demonstrated that calcium supplementation (any dose) is associated with a 45% reduction in the risk of pre-eclampsia (RR 0.45, 95% CI 0.31–0.65) and an absolute risk reduction of hypertension (RR 0.65, 95% CI 0.53–0.81), as well as reducing severe morbidity in mothers. In addition, the Cochrane review found that 11 trials with 15,275 women demonstrated that calcium supplementation reduced the average risk of preterm birth (RR 0.76, 95% CI 0.60–0.97) (see Calcium evidence profile 1).

Another systematic review published in *BMJ Clinical Evidence* also observed that calcium supplementation is beneficial in pregnant women at risk of pre-eclampsia.¹⁶¹ The evidence further demonstrated no overall effect on the risk of stillbirth or infant death or admission of the baby into intensive care.^{158,161} However, some authors note that the moderate quality of evidence limits the usefulness of this intervention¹⁶² (see Calcium other evidence table).

Effect of risk prevalence

The Cochrane review observed a larger risk reduction among those with low calcium diets (RR 0.36, 95% CI 0.20–0.65) (see Calcium evidence profile 2) and those at high risk (RR 0.22, 95% CI 0.12–0.42) (see Calcium evidence profile 3). Although most trials in this systematic review were of good quality, these studies have noted that the small size of studies and publication bias may affect the results.

Effect of timing and dose

The evidence from the Cochrane review of the 10 trials demonstrated that supplementation with low doses of calcium (<1 g/day) significantly reduced the risk of pre-eclampsia (RR 0.38, 95% CI 0.28–0.52) along with hypertension, low birthweight and admission to a neonatal intensive care unit. The quality of evidence, however, is low so these findings need to be confirmed with larger, high-quality studies.

No evidence is available about how the timing of starting calcium supplements may impact on effectiveness; again, further research in this area is needed. The WHO currently recommends starting at 20 weeks and continuing until birth, but ongoing research, such as the CAP¹⁶³ and AMCAL¹⁶⁴ studies, is examining the effect of starting supplementation early in pregnancy or even pre-conception, based on the hypothesis that the prophylactic effect will be better if started earlier in pregnancy.

Adverse effects and safety

The Cochrane review showed an anomalous increase in the risk of HELLP syndrome among those supplemented with calcium in two trials (12,901 women; RR 2.67, 95% CI 1.05–6.82). However, the absolute number of events was low (16 vs 6).¹⁵⁸

One study in The Gambia noted rebound postnatal bone demineralisation following calcium supplementation in women with low intake. However, the quality of this evidence was low.^{158,165} It also noted having large doses of calcium (1–2 g of elemental calcium – usually in three or four tablets) that are difficult to swallow can interrupt supplementation.^{94, 161,166}

Numbers needed to treat

Overall, the NNT with calcium supplementation to prevent one case of pre-eclampsia in the general population is 28. In women at high risk of pre-eclampsia, the NNT is 7.¹⁵⁸

Other factors

Other factors include women's preferences and cost-effectiveness.

- Researchers note high-dose calcium tends to be unpalatable, making the woman's preferences and likely compliance an important consideration, and other formulations are available.
- Consider the calcium content of any other vitamin supplements the woman is taking.

Evidence statement:

Antihypertensive drugs

Antihypertensives – recommendations

- Urgently treat all women with severe hypertension (dBP \geq 110 or sBP \geq 160) with antihypertensives to acutely lower blood pressure.
Strong recommendation; low-quality evidence
- Consider antihypertensives for women with gestational hypertension (dBP \geq 90 or sBP \geq 140), especially those with risk factors and/or co-morbidities.
Strong recommendation; very low-quality evidence
- As well as taking account of the evidence and clinical experience, consider the choice of antihypertensive drug in the context of resource availability, the local health care setting and the condition of the individual woman.
Strong recommendation; very low-quality evidence
- Emphasise educating women so that they clearly understand the importance of taking their antihypertensive drugs as prescribed, the symptoms of HDP and when to report symptoms.
Weak recommendation; very low-quality evidence
- First-line antihypertensives to use in treating HDP include: labetalol, nifedipine and methyldopa.
Strong recommendation; very low-quality evidence

Introduction

Blood pressure is the product of both cardiac output and vascular resistance. In a healthy pregnancy, cardiac output increases to provide extra blood and oxygen for the growing fetus. Vascular resistance decreases at the same time, keeping blood pressure approximately normal. Hypertension can be produced by vasoconstriction (increased vascular resistance) or increased cardiac output.^{167,168}

Antihypertensives work by causing vasodilation (such as calcium channel blockers) or by reducing cardiac output (eg, by reducing heart rate, such as with beta-blockers). Reducing cardiac output or blood pressure can potentially compromise the fetus.¹⁶⁹

Controlling mild to moderate hypertension may not prevent progression to pre-eclampsia, but it is desirable in reducing the risk of poor maternal outcomes such as a cerebrovascular accident (CVA) or stroke. The type of antihypertensive drug may vary in its fetal effects. For example, some beta-blockers are associated with intrauterine growth restriction (IUGR) (where labetalol have the least impact). In contrast, calcium channel blockers may be associated with reduced IUGR, but they are also linked with fetal tachycardia.¹⁷⁰

In addition to haemodynamic changes, pregnancy is associated with changes in the clearance of most antihypertensive agents. These changes impact the choice of pharmacological agents and may require modifications in dosage and dosing interval. In some cases, the greater variability among women makes it necessary to individualise dosing based on clinical response and to balance pharmacodynamic effects so that both mother and fetus benefit.¹⁶⁹

Categories of hypertensive drugs for pregnancy

Calcium channel blockers and beta-blockers are the drugs of choice in pregnant women for blood pressure control. Research shows they are safe and effective in pregnancy. However, no strong evidence suggests that one class of antihypertensive drugs is better than another.¹⁷¹ Methyldopa (an indirect agonist for alpha2-adrenergic receptors) is another commonly used drug for hypertension in pregnancy. However, it is slower to act than some other calcium channel blockers or beta-blockers.³¹

Contraindicated: Women should not normally use ACE inhibitors and angiotensin receptor blockers in pregnancy because they potentially have harmful fetal effects (see ‘Adverse effects and safety’). This guideline excludes them from the discussion of evidence and reference to ‘any hypertensive class/drug’.

Antihypertensive drugs for the management of hypertension in pregnancy

Reducing the risk

The evidence for the effect of antihypertensive drugs is based on a Cochrane review of 49 trials (4,723 women) and is of moderate to low quality.¹⁷¹ In this Cochrane review, evidence from 29 trials demonstrated that treatment of mild to moderate hypertension with any agent (when assessed as a group) halves the risk of severe hypertension (RR 0.49, 95% CI 0.40–0.60) (see Antihypertensives evidence profile 1). However, the analysis suggests that treatment with antihypertensive drugs does not reduce the risk of developing pre-eclampsia (RR 0.93, 95% CI 0.80–1.08) or any other maternal or fetal outcome¹⁷¹ (see Antihypertensives evidence profile 1). However, when antihypertensives were assessed in different types of mild to moderate hypertension, they were effective at reducing the risk of severe hypertension and pre-eclampsia (see Antihypertensives evidence profile 7).

Comparisons of medicines

There is no clear evidence suggesting that one class of antihypertensive drug is better than another and evidence shows no significant differential effects.¹⁷ When compared with no treatment, calcium channel blockers did not reduce the risk of developing pre-eclampsia or severe hypertension (see Antihypertensives evidence profile 3), but beta-blockers significantly reduced the risk of developing pre-eclampsia and severe hypertension (see Antihypertensives evidence profile 2), while methyldopa reduced the risk of developing severe hypertension (see Antihypertensives evidence profile 4).

However, the Cochrane review showed that when beta-blockers and calcium channel blockers were considered together, the overall risk of developing pre-eclampsia and severe hypertension decreased compared with methyldopa (11 trials, 997 women; RR 0.73, 95% CI 0.54–0.99) (see Antihypertensives evidence profile 5). There were no significant differences between any outcomes when beta-blockers or glyceryl trinitrate were compared with calcium channel blockers (see Antihypertensives evidence profile 6).

Target blood pressure

This guideline does not recommend aggressively normalising blood pressure. The evidence from another Cochrane review (two trials, 256 women) indicates that in pregnant women with mild to moderate hypertension, very tight control of blood pressure (target level of 130/80 mmHg or less) was no better than tight control (below 140/90 mmHg) in holding back progression to severe hypertension (RR 1.28, 95% CI 0.97–1.7) or in outcomes for the baby (IUGR RR 1.09, 95% CI 0.65–1.82; admission to a neonatal intensive care unit RR 0.77, 95% CI 0.45–1.31)¹⁷² (see Antihypertensives evidence profile 8). The Control of Hypertension In Pregnancy Study (CHIPS), published since the Cochrane review, found that while tight control (target diastolic blood pressure, 85 mmHg) did not affect outcomes for infants, severe hypertension ($\geq 160/110$ mmHg) developed in 41% of the women in the less-tight-control group and 28% of the women in the tight-control group ($p < 0.001$).¹⁷³

Harm

While the Cochrane studies offer no clear evidence on how fetal outcomes benefit from antihypertensive treatment in women with mild to moderate hypertension, other studies have observed an increased risk of IUGR and small for gestational age babies. The researchers have

attributed this finding to the effect of the hypertensive disease rather than the antihypertensive drug.^{174,175} However, two other retrospective studies found a high incidence of SGA in hypertension treated with beta-blockers. The first directly compared labetalol with nifedipine (38.8 vs 15.5 %, $p < 0.05$)¹⁷⁶ and the second compared any beta-blocker with methyldopa (AOR 1.95, 95% CI 1.21–3.15).¹⁷⁷

The current evidence is inconclusive as to whether antihypertensive therapy in mild to moderate hypertension prevents progression of disease or improves maternal and fetal outcomes. However, health professionals should consider the possible effects of long-term use of labetalol in pregnancy.

Recommendation – mild to moderate hypertension

Until further high-quality evidence is available, management decisions on whether antihypertensive treatment should be provided in mild to moderate hypertension in pregnant women and the choice of drug must be based on interpretation of current evidence, potential adverse effects, clinical experience and judgment, and specific to the individual woman and the effects on mother and baby¹⁷⁴.

Considering the above, the following findings apply to possible antenatal drug treatment for hypertension in pregnancy.

- All antihypertensive drugs appear to be equally effective for maintaining blood pressure within this target range.
- ACE inhibitors and angiotensin receptor blockers are not used in pregnancy because of their potential to harm the fetus (see ‘Adverse effects and safety’).
- Calcium channel blockers (eg, nifedipine) can be used and they may reduce the incidence of IUGR. However, less evidence is available about how effective and safe they are in pregnancy in comparison with labetalol.
- Beta-blockers (eg, labetalol) have conventionally been the first-line use for blood pressure control in pregnancy but evidence supporting their use is of low quality. Note that non-selective beta-blockers appear to have a negative impact on fetal growth.
- Methyldopa is a safe and effective antihypertensive in pregnancy. However, because it has central nervous system and hepatic side effects, it is usually not a first-line treatment.

Antihypertensive drugs for managing severe hypertension in pregnancy

Reducing the risk

It is commonly accepted that using antihypertensives (vs none) for severe hypertension reduces the risk of developing pre-eclampsia and stroke. A range of antihypertensives have demonstrated safety and efficacy; the most important consideration in choice of agent is that the health care team has experience and is familiar with that agent.

Comparison of medicines

A Cochrane review of 35 trials (3,573 women) compared the effects of calcium channel blockers (nifedipine), beta-blockers (labetalol), vasodilators (hydralazine) and the aromatic-amino-acid decarboxylase inhibitor methyldopa. It found that the evidence was insufficient to conclude that any one antihypertensive drug is more effective or safer than another¹⁷⁵ (see Antihypertensives evidence profiles 9–12).

However, the evidence from this Cochrane review demonstrated that women allocated calcium channel blockers were less likely to have persistent high blood pressure compared with those allocated hydralazine (six trials, 313 women; 8% vs 22%, RR 0.37, 95% CI 0.21–0.66) (see Antihypertensives evidence profile 9).

Alternative hypertensive drugs seem better than methyldopa for reducing the risk of severe hypertension (11 RCTs, 638 women; RR (random effects) 0.54, 95% CI 0.30–0.95, risk difference (RD) –0.11 (–0.20 to –0.02), numbers needed to harm (NNTH) 7 (5–69)).³¹ Studies have found no significant differences in maternal or fetal outcomes with the different antihypertensive drugs^{175,178} (see Antihypertensives other evidence table).

The evidence from another systematic review of 15 RCTs (of 915 women) demonstrated that nifedipine capsules (10 mg orally), compared with nifedipine sustained-release tablets (10 mg orally), were associated with more maternal hypotension (<110/80 mmHg) at 90 minutes (35% vs 9%; RD 0.26; 95% CI 0.07–0.46, one trial, 64 women).¹⁷⁸ When studies compared short-acting nifedipine with intravenous hydralazine in pregnancy, they observed no significant difference in effectiveness (achievement of target BP (84% [nifedipine] vs 79% [hydralazine], RR 1.07, 95% CI 0.98–1.17; five trials, 273 women), the time taken to achieve the target BP (weighted mean difference) (1.36 hours, 95% CI 6.64–4.14), or the need for a repeat dose(s) of antihypertensive (51% vs 55%, RR 0.97, 95% CI 0.50–1.88; four trials, 246 women)).¹⁷⁸

In this review, the evidence from a single trial (74 women) that compared oral labetalol 100 mg four times daily with oral methyldopa 250 mg four times daily showed no significant difference in achievement of target BP (47% versus 56%, RR 0.85, 95% CI 0.54–1.33). The study found no significant differences in maternal hypotension between these different drugs (RR 0.05, 95% CI –0.03 to 0.12) or other adverse maternal and fetal outcomes.¹⁷⁸ In severe hypertension, the risk of persistent high blood pressure was lower for a calcium channel blocker (nimodipine) compared with magnesium sulphate (two trials, 1,683 women; 47% vs 65%, RR 0.84, 95% CI 0.76–0.93). However, these two medicines did not differ significantly in changing the risk of developing eclampsia¹⁷⁵ (see Antihypertensives evidence profile 13).

Number needed to treat

The GDT found no number needed to treat statistic in the literature for poor maternal outcomes (eg, CVA/stroke) in the presence of severe hypertension (not pre-eclampsia). One study noted that labetalol was related to fewer caesarean sections, with an NNT of 3.3 no matter which drug researchers compared it with.¹⁷⁹

Recommendation – severe hypertension

The evidence suggests calcium channel blockers (nifedipine), beta-blockers (labetalol) and vasodilators (hydralazine) are suitable options for treating severe hypertension in pregnancy and postpartum. However, the current evidence is of moderate to low quality. Until further evidence is available, clinicians need to base the choice and route of administration of antihypertensive drugs in managing severe hypertension on the availability of the drugs, their own experience, the individual woman's condition, her compliance with administration and the local health care setting.

The GDT could identify no evidence to determine the level of severe hypertension to start treatment to prevent severe maternal complications or on the acute management of severe hypertension. In this situation, the information available is based on expert opinion, usually provided in the clinical guidelines. Box 2 sets out suggested treatment regimens for the acute management of severe hypertension in the ACOG³⁴ and SOMANZ³¹ guidelines.

Box 2: Antihypertensive agents for acute lowering of severe hypertension

Nifedipine

10 mg conventional release tablet (oral)

Onset of action: 30–45 minutes

Onset of maximum effect: 30 minutes

Repeat: after 30–45 minutes (if needed)

Maximum: 80 mg daily

Labetalol

Initially 20 mg IV bolus over 2 minutes

Onset of action: 5 minutes

Onset of maximum effect: 10–15 minutes

Repeat with 40–80 mg

Repeat: every 10 minutes (if needed)

Maximum: 300 mg

Hydralazine

5–10 mg IV bolus over 3–10 minutes (5 mg if fetal compromise)

Onset of action: 20 minutes

Onset of maximum effect: 10–80 minutes

Repeat: every 20 minutes

Maximum: 30 mg

Consider IV bolus of crystalloid fluid before or when administering first IV hydralazine dose (usually 200–300 mL)

HELLP syndrome

The evidence does not demonstrate any reduction in the risk of developing HELLP through using antihypertensive drugs.¹⁷⁵

Adverse effects and safety

ACE inhibitors are contraindicated in pregnancy because they can have adverse fetal effects. Oligohydramnios, renal failure, bony malformations and prolonged hypotension have been associated with the use of ACE inhibitors in the second and third trimesters of pregnancy. However, they are useful postpartum, and specific drugs (eg, enalapril) have been proven safe while breastfeeding.

Evidence suggests that teratogenicity or toxicity may be a problem if a woman becomes pregnant while taking an ACE inhibitor.^{180,181} A cohort study found infants exposed to ACE inhibitors in the first-trimester had an increased risk of major congenital malformations (RR 2.71, 95% CI 1.72–4.27).¹⁸⁰ A systematic review of ACE inhibitor use in pregnancy (analysed by trimester exposure) also found that there is a risk of teratogenicity with exposure during the first trimester but less risk than that of secondary third trimester exposure.¹⁸² In discussing the risks and benefits of continuing ACE inhibitors, a review notes that women with, for example, chronic kidney disease may benefit from continuing to use ACE inhibitors until pregnancy is confirmed.¹⁸³ Therefore, a woman planning to become pregnant should discuss switching to an alternative hypertensive with her specialist in anticipation of becoming pregnant. When pregnancy is confirmed for any woman taking an ACE inhibitor, her GP or an obstetric consultant should prescribe her an alternative drug (following the Referral Guidelines).¹⁰²

The evidence from the Cochrane reviews on using antihypertensive drugs in mild to moderate hypertension and severe hypertension also did not show any significant differences in maternal or fetal outcomes in the various antihypertensive agents.^{171,175} However, a cohort study of 1,418 women who reported using antihypertensive drugs in early pregnancy found an increased risk of infant cardiovascular defects (OR 2.59, 95% CI 1.92–3.51). Stillbirth rate also increased (RR 1.87, 95% CI 1.02–3.02), again without any clear differences between the drug used.¹⁸⁴ Although a dose effect is present in the pharmacological treatment of hypertension, there is little evidence on dose effect on potential short-term complications such as fetal growth or long-term outcomes of children born to women who were treated or not treated for their hypertension.¹⁶⁹

The limitations in evidence suggest that clinical judgement must consider adverse effects and contraindications of specific drugs. For instance, one side effect of methyldopa is depressed mood, which makes it perhaps not the best choice in long-term antenatal or postpartum control of hypertension.³¹ Also in the postpartum period, hypotension may be a side effect in the neonate of the breastfeeding woman.³³

Postpartum

The evidence for antihypertensive treatment postpartum comes from a Cochrane review of nine RCTs (838 women).⁵⁷ The results showed no significant reduction in the risk of severe hypertension (RR 0.91, 95% CI 0.6–1.39) and were inadequate to make definitive conclusions (see Antihypertensives evidence profile 14). In this review, use of additional hypertensives (compared IV hydralazine with sublingual nifedipine and methyldopa) for postpartum hypertension (severity not defined) showed no significant difference (RR 0.70, 95% CI 0.25–1.96; three trials, 309 women) and the drugs were well tolerated, but the trials were not consistent in their effects (see Antihypertensives evidence profile 15). Subgroup analysis in this review showed no significant differences in the use of additional antihypertensive therapy (RR 0.92, 95% CI 0.20–4.20; three trials, 189 women) for mild to moderate hypertension. In severe postpartum hypertension, two trials (120 women) demonstrated that use of additional antihypertensive therapy did not differ between groups (RR 0.58, 95% CI 0.04–9.07; two trials, 120 women) and found no maternal deaths or hypotension.⁵⁷

As it has been demonstrated that peak postpartum blood pressure occurs between days three and six postpartum, clinicians should be aware that peaks may occur after hospital discharge and, therefore, health professionals may miss a concerning rise in blood pressure unless they ensure women have close follow-up.³²

Research has produced weak evidence on the compatibility of antihypertensive drugs and breastfeeding and clinical outcomes for the baby. In the absence of evidence, expert opinion is to continue breastfeeding because most of the commonly used antihypertensive drugs appear to be safe for the baby and the benefits of breastfeeding outweigh potential risks to the baby of transferring antihypertensive drugs in breast milk.³³ Health professionals do need to consider the gestational age of the baby as evidence has shown preterm babies have an increased risk of adverse effects compared with those born at term.¹⁸⁵

Evidence statement: Maternal and fetal monitoring

Maternal and fetal monitoring – recommendations

Antenatal monitoring

- Educate women (and their families and whānau) fully around the need to contact their LMC urgently if they experience symptoms of pre-eclampsia. These symptoms include:
Strong recommendation; very low-quality evidence
 - severe headache
 - problems with vision, such as blurring or flashing before the eyes
 - severe epigastric pain or right upper quadrant pain
 - vomiting
 - sudden swelling of the face, hands or feet.
- A woman presenting with features of pre-eclampsia requires urgent (same day) referral to an obstetric specialist and a transfer of care (referral code 4022). Usually the woman will be admitted to hospital.
Strong recommendation; very low-quality evidence
- For women managed as outpatients, base the frequency of additional antenatal appointments (from the conventional appointment schedule) on the woman's individual needs, the severity of her condition and her preferences.
Strong recommendation; very low-quality evidence
- Refer women with hypertension in pregnancy for a full assessment by an obstetric specialist (referral code 4009). The specialist should make a plan for who is going to carry out the ongoing care and monitoring of the woman and her baby in conjunction with the woman, the LMC and GP.
Strong recommendation; very low-quality evidence

Postnatal monitoring

- Carefully monitor women with hypertensive disorders in pregnancy for increasing hypertension postpartum. Blood pressure frequently increases around three to five days after birth. Continue to monitor blood pressure frequently through the postnatal period.
Strong recommendation; very low-quality evidence
- Strict fluid balance should continue to be observed in severe pre-eclampsia.
Weak recommendation; low-quality evidence
- Monitor for all signs of pre-eclampsia (including pre-eclampsia bloods) returning to normal but beware of post-partum eclampsia.
Strong recommendation; high-quality evidence

Introduction

This evidence statement has two main parts: maternal monitoring and fetal monitoring. Support for monitoring women with hypertensive disorders in pregnancy comes from the high maternal and fetal adverse outcomes and the rapid progress to severe disease. However, the GDT found no evidence on the protocols of maternal monitoring and their effects on the maternal and fetal outcomes.

Maternal monitoring

The current monitoring regimes appear to rely on the evidence of the progression of disease so that 25–50% of women with gestational hypertension progress to pre-eclampsia and 10% progress to severe disease.^{186,187,188} Studies have demonstrated about 60% of women who had pre-eclampsia developed recurrent pre-eclampsia, but observed no association between the severity of the later experience and the severity of the previous disease.¹⁸⁹ As the aim of monitoring is to detect worsening disease to allow timely and appropriate intervention, the current expert opinion (NICE-UK) is that the routine schedule of antenatal assessment (of 10 appointments in nulliparous and seven in parous women) is not adequate for women with hypertensive disorders.^{31,32,33} However, one study observed no significant change in outcome among women with mild hypertension if care remained on the normal schedule range and in the hands of primary care.¹⁹⁰ No RCT was found on a particular schedule or place for maternal monitoring but expert opinion suggests customising modalities and schedules for monitoring to the individual woman.¹⁹¹

The current parameters of maternal monitoring focus on measurement of blood pressure, proteinuria, symptoms of pre-eclampsia, tests of systemic functions (hepatic, renal and coagulation) and symptoms indicative of interventions for birth.^{33,34,190}

Blood pressure

The device and technique of blood pressure measurement are important in diagnosing and monitoring hypertension in pregnancy. Although mercury sphygmomanometry is considered the gold standard, the evidence is not adequate to draw conclusions on the reliability of aneroid devices compared with mercury sphygmomanometers. Some studies have shown that 50% of aneroid devices had at least one reading that was more than 10 mmHg out, compared with only 10% of mercury devices.¹⁹² Others have shown that systolic pressure was higher with the automated device (mean difference 2.5 mmHg, 95% CI 1.9–3.2 mmHg), whereas diastolic pressure was higher with the mercury sphygmomanometer (mean difference 2.0 mmHg, 95% CI 1.5–2.6 mmHg).¹⁹³ Studies using calibrated automated devices tested in pregnant women show results comparable with those of mercury sphygmomanometers.¹⁹⁴

In view of the evidence, clinical practice guidelines and the ISSHP statement, this guideline recommends that any automated devices you use for blood pressure measurement should have demonstrated reliability for blood pressure measurement in pregnant women.¹

Blood pressure – device

It is recommended that Korotkoff phase 1 is appropriate to measure systolic blood pressure and Korotkoff 5 to measure diastolic blood pressure.¹⁹⁵ The systolic blood pressure is accepted as the first sound heard (K1) and the diastolic blood pressure as the disappearance of sounds completely (K5). Where K5 is absent, accept K4 (muffling).

Correct cuff size is important for accurately recording blood pressure. Use a large cuff with an inflatable bladder covering 80% of the arm circumference if the upper arm circumference is greater than 33 cm but less than 44 cm; use a thigh cuff if the upper arm circumference is greater than 44 cm.^{196,197} This practice helps to minimise overdiagnosis of hypertension during pregnancy as a cuff that is too small will overestimate blood pressure. Deflate the cuff at a rate of ≤ 2 mm per second as rapid deflation leads to underestimation of the systolic blood pressure.^{197,198}

An important aspect of blood pressure monitoring is accurate measurement using calibrated devices and appropriate cuff size. However, a study in New Zealand found that despite the protocol, health professionals often measured blood pressure using a standard cuff even in obese women.²⁰⁴

Randomised controlled trials offer no evidence on the effectiveness of alternative modalities of blood pressure measurement during pregnancy.¹⁹⁹ However, evidence from observational studies suggests that using 24-hour ambulatory blood pressure monitoring (ABPM) is the ideal way of making the diagnosis.^{200,201,202} Some observational studies have shown that ABPM correlates better with proteinuria than conventional sphygmomanometry and is a better predictor of hypertensive complications; they have also shown it is effective in differentiating white coat hypertension.^{200,203} However, the availability and cost of ABPM limit the extent to which it can be used; so this guideline suggests using the conventional blood pressure measurement at a clinical setting measured at least four hours apart.³²

Blood pressure – technique

The evidence for the optimum technique for blood pressure measurement is also limited, however. The current opinion is that blood pressure should be measured with the woman rested and seated at a 45-degree angle with the arm at the level of the heart. A study of 5,434 women has demonstrated that the variation in blood pressure between arms is usually less than 10 mmHg (inter-arm difference of at least 10 mmHg in systolic blood pressure was observed in 8% of pregnant women; for diastolic blood pressure, a similar variation in diastolic was observed in 2% of pregnant women).²⁰⁵ In labour, blood pressure measurement in the lateral position is considered to be appropriate, but researchers have noted that measuring blood pressure on the right arm with the woman in the left lateral position may give falsely lower recordings, as may measuring while she is in a supine posture (on her back).^{31,34}

Blood pressure – setting

The evidence from RCTs demonstrated that admitting a woman to hospital was not effective in preventing the progress of disease or adverse outcomes in non-severe cases.^{124,206} Furthermore, the evidence from observational studies shows that the prognostic value of home blood pressure monitoring is equal to or higher than that of office blood pressure monitoring.²⁰⁷ The results from an RCT (of 54 women) demonstrated that day-unit monitoring of women with hypertension in pregnancy significantly reduced the risk of severe hypertension (RR 0.58, 95% CI 0.38–0.89), the need for and the length of antenatal inpatient admissions and the number of medical interventions²⁰⁸ (see Monitoring evidence profile 1). An Australian study showed that using telemedicine in high-risk pregnancies increased the number of appointments the women kept and permitted timely referrals, as well as still permitting many women to deliver closer to their hometowns.²⁰⁹

Evidence of home-based antenatal monitoring by a midwife is not available. It may be acceptable to generalise the findings of day-unit monitoring to home- or community-based monitoring.

Proteinuria

Although the current evidence suggests that pre-eclampsia can present without proteinuria, proteinuria is a key parameter in diagnosing pre-eclampsia (see the evidence statement ‘Classifications and clinical definitions’). The current practice for monitoring for proteinuria is to use the dipstick as a screening test in the community setting and to verify with protein:creatinine ratio (PCR) if the dipstick test is positive (see the evidence statement ‘Classifications and clinical definitions’).

Many studies have compared the consistency of a PCR test with 24-hour urinary protein. A systematic review of protein tests in hypertensive pregnant women found PCR is a simple and practical indicator of proteinuria and points out the disadvantages of 24-hour urine collection, including delayed diagnosis and inaccuracy.⁴³ It also mentions that The National Kidney Foundation in the USA now recommends spot PCR tests (instead of 24-hour urine collection) to diagnose proteinuria in most situations.²¹⁰ Once proteinuria is established, this guideline does not recommend monitoring for severity of proteinuria as studies have not found that its level of severity predicts worsening of the disease.^{39,40,41}

Monitoring the systemic functions

This guideline recommends testing blood for renal function, liver function and platelet count at the time of diagnosis of new proteinuria or when a woman's blood pressure suddenly increases.^{31,32,191}

Several studies have shown that women with pre-eclampsia are at higher risk of venous thromboembolism (eg, deep vein thrombosis, pulmonary embolism) in the postnatal period. Using proportional hazards modelling to control for age and caesarean section, one study showed that, compared with all control groups combined, women with pre-eclampsia were 2.2 times more likely (95% CI 1.3–3.7) to be admitted to hospital with venous thromboembolism (VTE) postpartum.²¹¹ A large cohort study also found similar results, with relative rates of VTE of 1.84 (95% CI 0.59–5.78) in the postpartum period for women with pre-eclampsia.²¹²

A systematic review of risk factors for VTE in pregnancy provided further evidence that pre-eclampsia, in and of itself, does not affect the VTE risk during the antepartum period, whereas in the postpartum period, pre-eclampsia is associated with an increased VTE rate.²¹³ In light of this evidence, you should evaluate the need for postnatal preventive treatments for VTE using a recognised pregnancy VTE risk assessment tool,²¹⁴ such as those described in the RCOG *Thrombosis and Embolism during Pregnancy and the Puerperium Green-top Guideline*.²¹⁵

Monitoring the symptoms of pre-eclampsia

Common advice for women at risk of, or with, hypertensive disorders in pregnancy is to self-monitor symptoms of pre-eclampsia (epigastric pain, headache, blurring of vision or flashing spots in front of the eyes, nausea or vomiting, or sudden swelling of the face, hands or feet).²⁰⁵ The results from an observational study suggest the usefulness of a scale based on a checklist of 11 symptoms (nausea, blurred vision, inability to concentrate, malaise, vertigo, epigastric pain, persistent headache, headache unrelieved by rest or paracetamol, headache with nausea and/or vomiting, headache with blurred vision or scotoma (Pre-eclampsia Prenatal Symptom-Monitoring Scale-PPSMC-11)) in practice, rather than the usual assessment with the conventional five symptoms.²¹⁶ The results of logistic regression of the PPSMC-11 (in a study of 100 women) demonstrated that the scale was a significant predictor of worsening pre-eclampsia and gestational hypertension (OR 1.22, 95% CI 1.07–1.49, $p = 0.04$)²¹⁶. However, PPSMC-11 is not currently used in clinical practice and needs further research on its effectiveness in preventing adverse outcomes.

Another model that research has shown is useful in clinical practice is the Pre-eclampsia Integrated Estimate of RiSk (PIERS) model. The evidence from an observational study using the full PIERS model demonstrated that the model identifies women at increased risk of adverse outcomes up to seven days before.⁵³ Predictors of adverse maternal outcomes included gestational age, chest pain or dyspnoea, oxygen saturation, platelet count, and creatinine and aspartate transaminase concentrations. The full PIERS model predicted adverse maternal outcomes within 48 hours of study eligibility (AUC ROC 0.88, 95% CI 0.84–0.92).⁵³

Researchers revised this model and tested a miniPIERS model, which showed benefit in supporting the capacity of community-level health care providers to assess the risk in women with pregnancy hypertension.²¹⁷ This miniPIERS model is limited to demographics, symptoms and signs (parity (nulliparity vs parity), gestational age on admission, headache/visual disturbances, chest pain/dyspnoea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria). It was well calibrated and has an AUC ROC of 0.77 (95% CI 0.74–0.80). A predicted probability of $\geq 25\%$ to define a positive test classified women with 85.5% accuracy.²¹⁷ However, the miniPIERS model is not widely used in clinical practice and no RCTs have compared its effectiveness with other models based on symptoms.

Frequency of maternal monitoring

Even though no studies have assessed the benefits and risks of different maternal monitoring modalities, in clinical practice the frequency of monitoring usually depends on the severity of hypertension or pre-eclampsia, gestational age at time of diagnosis and fetal growth findings. The common clinical practice prescribes weekly monitoring of blood pressure and testing for proteinuria when hypertension is mild, and monitoring twice a week when hypertension is moderate, as well as monitoring for the symptoms of pre-eclampsia and fetal movements.^{31,32,218} This guideline recommends monitoring organ function weekly with laboratory tests (urine protein, serum creatinine, platelet count and liver enzymes) and also, at the time of diagnosis of pre-eclampsia, or when symptoms of worsening disease occur, or every two to three weeks, assessing the fetus. It also advises that women monitor fetal movements and report immediately if they develop vaginal spotting, abdominal pain or uterine contractions.^{31,32} The frequency of monitoring in severe cases depends on how severe the conditions are.²¹⁷

Postpartum monitoring is also critical in women with hypertensive disorders, as evidence that indicates the prevalence of de novo postpartum hypertension or pre-eclampsia is between 0.3% and 27.5%, but it is unlikely to present after the fifth day.²¹⁸ Further evidence shows that blood pressure in women with pre-eclampsia decreases within 48 hours of giving birth but increases again between three and six days postpartum.

New onset hypertension may also arise in the postpartum period in women who did not have hypertension in the antenatal period. This could be a non-specific phenomenon but may also be late onset pre-eclampsia or the unmasking of chronic hypertension. Therefore, advise women with pre-eclampsia, especially complicated or severe disease, to stay in a secondary or tertiary facility for at least 72 hours postpartum, which can monitor their blood pressure and conduct relevant laboratory investigations.³³ Using nonsteroidal anti-inflammatory drugs (NSAIDs) postpartum involves a theoretical risk. Avoiding using them for pain relief may help control persistent hypertension, as these drugs may increase blood pressure and adversely affect kidney function. One study, however, found that when women that had severe hypertensive disorders took NSAIDs, it was not associated with a difference in the average mean arterial pressures postpartum.²¹⁹

Referral

The current clinical practice guidelines identify worsening of hypertension at any stage of pregnancy as a requirement for referring a woman to a hospital setting to assess maternal organ dysfunction and the fetus.^{31,206} The benefit of admitting women for this purpose is that it is possible to individualise appropriate assessment of maternal and fetal status to the woman and makes it easier for those involved in the woman's care to have three-way communication and discussion. As such, you need to consider the criteria of the New Zealand Referral Guidelines¹⁰² for women with pre-existing hypertension (referral code 1014, 1015) and previous pre-eclampsia (referral code 3008) in relation to the monitoring modalities. Research shows that, in non-severe cases, out-of-hospital assessment, such as at a day assessment unit, is effective.³² For this reason, in non-severe cases, the place for monitoring maternal condition needs to consider the location of the woman in relation to an appropriate facility, resources available and the woman's preference for complying with monitoring requirements.

Fetal monitoring

Although hypertensive disorders in pregnancy are one of the most common indications for fetal surveillance, evidence about specific modes of assessing the status of the fetus in this context is limited. Furthermore, the timing and frequency of testing have not been adequately evaluated, which is another limitation on evidence on these aspects.²²⁰ With the limitations on evidence, the current practices are based on experience, opinion and clinical experience in different care settings. The discussion that follows is mainly drawn from existing clinical practice guidelines.^{31,32,33, 34,221}

Fetal monitoring in hypertensive disorders in pregnancy involves assessing fetal activity including fetal growth, movement, amniotic fluid volume, biophysical profile, fetal heart rate and cardiovascular parameters.^{220,223} It also involves evaluating placental function, transport and perfusion.

Assessing fetal growth

Intrauterine fetal growth restriction (FGR) is a clinical manifestation of severe hypertension and pre-eclampsia. Significant FGR is a warning that a fetus is at greater risk of distress and indicates the need to increase fetal surveillance.²²⁴ It is imperative to identify any growth issues early: one study showed that infants that were not identified as being small for gestational age before birth were at a four times greater risk of adverse fetal outcome (OR 4.1, 95% CI 2.5–6.8).²²⁵

In practice, at community level, health professionals often use fetal growth to assess symphysio-fundal (SF) height, but SF height has a high false positive rate for detection of FGR. In a systematic review of eight studies, the sensitivity of SF height measurement for SGA (birthweight <10th percentile) prediction ranged from 0.27–0.76 and specificity ranged from 0.79–0.92.²²⁶ Evidence from an observational study demonstrated that antenatal detection rate of SGA doubled (50.6%) when serial plotting of fundal height on a customised growth chart – such as the Gestational Related Optimum Weight (GROW) chart – was compared with a record in clinical notes but not plotted on a chart (24.8%).²²⁷

However, another RCT demonstrated that fetal growth assessment with ultrasound has a higher sensitivity and specificity for detecting fetal growth restriction compared with SF height (sensitivity, 100% vs 42.86%; specificity, 92.62% vs 85.24%).²²⁸ No studies have looked at the effectiveness of ultrasound biometry specifically in pregnant women at risk of or with hypertensive disorders. However, based on the evidence from other studies, taken together with the risk of FGR associated with hypertensive disorders in pregnancy, this guideline recommends using ultrasound to assess serial fetal growth.

This guideline further suggests that women at high risk of SGA (including chronic and pregnancy-induced hypertension) should have serial growth scans scheduled as part of their secondary care pathway. For women identified as at high risk of pre-eclampsia, conducting an uterine artery Doppler assessment at 20–24 weeks is valuable. The results will help to establish a schedule for serial assessment of fetal size and, if the result is abnormal, a recommendation for an umbilical artery Doppler from 26–28 weeks.^{78,229} While this assessment has limited predictive value even in high-risk populations, a reassuring uterine artery Doppler study result may indicate fewer ultrasound evaluations can be performed during the pregnancy, while an abnormal outcome would suggest more intensive surveillance^{230,231} (see also ultrasound markers in the evidence statement on ‘Prediction – biomarkers and ultrasonographic markers’).

Assessing fetal status and distress

Fetal movement

Common advice is for caregivers to monitor fetal movement and mothers often use this spontaneously to assess the baby’s wellbeing. However, the GDT found no specific evidence in relation to pregnant women with hypertensive disorders.

A population-based study of 691 women demonstrated that low maternal awareness of fetal activity was associated with an increased risk of having a small for gestational age infant (OR 6.5, 95% CI 3.5–12.3) and receiving information about fetal activity was associated with increased maternal awareness (OR 2.0, 95% CI 1.2–3.4).²³² A Cochrane review of four studies involving 71,370 women compared providing women with a formal method of counting fetal movement with providing them with other methods of counting and providing no instructions.²³³ The findings indicated women were

significantly more likely to comply with the Cardiff ‘count to 10’ (once a day) method than the method where women were counting fetal movement 30 minutes before meals and at bedtime (more than once a day) (see Monitoring evidence profile 3). However, none of the studies compared the effects of fetal movement counting selectively or routinely with no counting on perinatal outcome; as such, the reviewers could neither confirm nor refute the effectiveness of counting fetal movements as a method of fetal surveillance.²³³ Similarly, the evidence is insufficient on the management strategies for decreased fetal movements such as vibroacoustic stimulation (VAS/mFBP) or mock stimulation for women whose babies are thought to be at risk of compromise for various reasons²³⁴ (see Monitoring evidence profile 4).

Biophysical profile

Although health professionals have used the biophysical profile (BPP) clinically for decades, evidence is currently inadequate to support this practice in high-risk pregnancies. A BPP includes ultrasound monitoring of fetal movements, fetal tone and fetal breathing, and ultrasound assessment of liquor volume with or without assessment of the fetal heart rate.

A Cochrane review²³⁵ of five trials (2,974 women) does not support using BPP as a test of fetal wellbeing in high-risk pregnancies. This review found no significant differences between the groups in perinatal deaths (RR 1.33, 95% CI 0.60–2.98) or in Apgar score less than seven at five minutes (RR 1.27, 95% CI 0.85–1.92)²³⁵ (see Monitoring evidence profile 5). Evidence from a study using the PIERS database suggests that the BPP has a limited role in the fetal assessment for pregnancies complicated by pre-eclampsia. The study found no evidence that the addition of ultrasound components of the BPP to a non-stress test and cardiotocograph (CTG) led to more accurate predictions of neonatal outcomes for women with pre-eclampsia.²³⁶

Non-stress tests, cardiotocograph

The non-stress test and CTG evaluate variations in fetal heart rate and the presence of accelerations as well as decelerations reflecting the underlying fetal status. Again the evidence available is not specific to women with hypertensive disorders in pregnancy.

Studies show the non-stress test has a negative predictive value of 99% for fetal status. However, evaluations of the non-stress test and CTG have linked them to a trend of increasing perinatal deaths, raising questions about whether using them is advisable.²²⁰ One RCT of 1,360 women compared the effectiveness of umbilical artery Doppler testing and non-stress testing for fetal assessment for a range of conditions, including hypertension.²³⁷ Its findings demonstrated that umbilical artery Doppler as a screening test for fetal wellbeing in high-risk pregnant women was associated with a decreased incidence of caesarean birth for fetal distress compared with the non-stress testing, while neonatal morbidity did not increase (see Monitoring other evidence table).

Doppler velocimetry

Doppler velocimetry evaluates the uteroplacental and the fetal circulation. Because it can evaluate, non-invasively, the uterine and placental vasculature, this tool has also been used to assess fetuses from high-risk pregnancies, including fetal growth restriction and pre-eclampsia (particularly early onset disease).²²⁰

Doppler velocimetry in clinical practice includes assessing umbilical artery and uterine artery flow velocity, and less frequently middle cerebral artery, ductus venosus and umbilical vein flow. The evidence indicates that these assessments differ in their contributions: the uterine artery Doppler indices are better predictors of maternal adverse outcomes while umbilical artery Doppler indices are better for assessing fetal adverse outcomes and more useful in managing FGR.²³⁸

Uterine artery Doppler

A systematic review of 74 studies of pre-eclampsia (total 79,547 women) and 61 studies of intrauterine FGR (total 41,131 women) compared different Doppler indices of uterine artery velocimetry. It demonstrated that the technique allows more accurate prediction of maternal and fetal adverse outcomes when performed in the second trimester than in the first-trimester.⁷⁸ This review also demonstrated that abnormal uterine artery waveforms are a better predictor of pre-eclampsia than of intrauterine FGR. However, it noted that an increased pulsatility index (PI) with notching was the best predictor of pre-eclampsia (LR+21.0 among high-risk women and 7.5 among low-risk women) as well as of overall (LR+9.1) and severe (LR+14.6) intrauterine growth restriction among low-risk women.⁷⁸

Umbilical artery Doppler

A Cochrane review reported that umbilical artery Doppler ultrasound in high-risk pregnancies (including hypertensive disorders) reduced the risk of perinatal deaths (RR 0.71, 95% CI 0.52–0.98) and resulted in fewer inductions of labour (RR 0.89, 95% CI 0.80–0.99) and fewer caesarean sections (RR 0.90, 95% CI 0.84–0.97). Due to the low quality of the current evidence, the authors of this review recommended interpreting results with some caution²²² (see Monitoring evidence profile 2).

Other Doppler studies

Another cohort study (of 168 women) assessed the predictive value of adverse perinatal or maternal outcomes in pre-eclamptic women of three ratios from Doppler velocimetry: middle cerebral to umbilical arteries pulsatility indices; middle cerebral to uterine arteries PI; and uterine to umbilical arteries PI. The findings showed that the middle cerebral to uterine arteries PI ratio was the only statistically significant index in multivariate analysis, demonstrating that this index is more accurate than other indices in predicting maternal and prenatal outcomes in pregnant women with pre-eclampsia.²³⁹

Frequency of fetal monitoring

A Cochrane review on fetal surveillance regimens identified one trial (of 167 women, 24–36 weeks) that compared two groups undergoing the same surveillance regimen (biophysical profile, non-stress tests, umbilical artery and middle cerebral artery Doppler and uterine artery Doppler) with the difference that one group was assessed twice a week and the other was assessed fortnightly (both groups had growth assessed fortnightly).²⁴⁰ The researchers concluded that data was insufficient to assess the review's primary infant outcome of composite perinatal mortality and serious morbidity (although there were no perinatal deaths) and they found no difference in the primary maternal outcome of emergency caesarean section for fetal distress (RR 0.96, 95% CI 0.35–2.63). In keeping with the more frequent monitoring, mean gestational age at birth was four days less for the twice-weekly surveillance group compared with the fortnightly surveillance group (mean difference –4.00, 95% CI –7.79 to –0.21). Women in the twice-weekly surveillance group were 25% more likely to have an induced labour than those in the fortnightly surveillance group (RR 1.25, 95% CI 1.04–1.50) (see Monitoring evidence profile 6). Some evidence indicates that fetal surveillance in a day assessment setting could be as effective as inpatient surveillance when blood pressure is well controlled and if women have no other complications.^{241,242}

A recent RCT (the TRUFFLE study) involved 503 women who had very preterm (26–32 weeks) growth-restricted babies. It compared two fetal surveillance methods – CTG short-term variation and fetal ductus venosus Doppler waveform (DV) – and their impact on timing of birth. While the difference in the proportion of infants surviving without neurological impairment was non-significant in relation to timing of birth, the researchers suggested that using late changes in DV might produce an improvement in developmental outcomes at two years of age. This study indicated a promising area for further research around short-term variability by electronic analysis of CTG and fetal DV for monitoring early preterm infants (26–32 weeks).²⁴³

Summary

In summary, there is limited evidence from high-quality studies to inform best practice for fetal surveillance modalities or regimens for managing women with hypertensive disorders in pregnancy. However, the high risk of intrauterine fetal growth restriction and adverse fetal outcomes in pregnant women with hypertension has prompted expert opinion to include fetal surveillance in the clinical management of these women. Current clinical practice is to assess fetal growth at the time of diagnosis and, in non-severe cases, to evaluate fetal growth every three to four weeks.^{31,33,34} In severe forms of the disease, much closer surveillance is appropriate, which includes more frequent umbilical artery Doppler evaluations and CTGs.^{220,244}

Where they identify SGA, health professionals may look for guidance on management from the New Zealand Maternal Fetal Medicine Network's SGA Guidelines.²²¹ While these are not official national Ministry of Health guidelines that the New Zealand maternity sector has ratified through a multidisciplinary process,²⁴⁵ secondary and tertiary facilities frequently use them as their default guidelines.

Other factors: women's preference and local setting

Women's preferences are an important aspect that you need to consider in advising them about maternal and fetal surveillance. Advice to women needs to be clear on the choices available to them and benefits and risks around the surveillance modalities; you also need to individualise it to each woman's situation. This is important as some studies have shown that the support pregnant women received from staff and labour companions was more important than the type of monitoring used.^{246,247}

Also consider the maternity care model in New Zealand needs in prescribing maternal and fetal monitoring modalities and frequencies. Part of this is to consider guidance for fetal monitoring in a rural setting in addition to guidance in a hospital setting.

Evidence statement:

Magnesium sulphate

Magnesium sulphate – recommendations

- Administering magnesium sulphate is clinically indicated to prevent another seizure in women with eclampsia, unless contraindicated.
Strong recommendation; high-quality evidence
- Also consider using magnesium sulphate to prevent a primary seizure in women with severe pre-eclampsia. However, the treatment priority is blood pressure control.
Weak recommendation; high-quality evidence
- Settings administering magnesium sulphate should have available one-to-one care, close monitoring and resuscitation/reversal medications (calcium gluconate).
Strong recommendation; very low-quality evidence
- For settings that cannot administer the full magnesium sulphate regimen, this guideline recommends using a loading dose IM or IV (see protocol) and then immediately transferring the woman to a higher-level health care facility.
Strong recommendation; low-quality evidence
- Continue magnesium sulphate for 24 hours following birth or 24 hours after the last seizure, whichever is the later.
Strong recommendation; very low-quality evidence

Introduction

Understanding is limited about the mechanism of action for magnesium sulphate in preventing and treating eclamptic seizures.²⁴⁸ The evidence indicates that this drug treats eclampsia through its effect on several cardiovascular and neurological functions and by altering calcium metabolism.^{249,250,251} Some studies have suggested that magnesium sulphate acts as a vasodilator, having actions that reduce vasoconstriction, protect the blood-brain barrier, decrease cerebral oedema formation^{252,253} and act as a cerebral anticonvulsant.²⁴⁹

Overall effect

Prophylaxis

The evidence for the effectiveness of magnesium sulphate comes from a Cochrane systematic review of 15 RCTs (including the Magpie trial of 2002) involving 11,444 women. It demonstrated that using magnesium sulphate as a preventative measure more than halved (59%) the risk of eclampsia, which was a statistically significant reduction (RR 0.41, 95% CI 0.29–0.58) compared with placebo or no anticonvulsant.²⁵⁴ However, the reduction in the risk of maternal death was not significant (RR 0.54, 95% CI 0.26–1.10).²⁵⁴ The two trials in this Cochrane review (10,332 women) that reported composite outcome of serious maternal morbidity showed no clear difference (RR 1.08, 95% CI 0.89–1.32). The risk of placental abruption was reduced for women allocated magnesium sulphate (RR 0.64, 95% CI 0.50–0.83; RD –0.01, 95% CI –0.02 to 0.00; NNT for an additional beneficial outcome 100, 95% CI 50–1,000) rather than placebo or no anticonvulsant.

For the baby, the evidence from this Cochrane review demonstrated no clear difference in the risks of perinatal death (RR 1.04; 95% CI 0.93–1.15) or admission to a special care baby unit (RR 1.01, 95% CI 0.96–1.06) between magnesium sulphate and a placebo²⁵⁴ (see Magnesium sulphate evidence profile table 1).

As a treatment

Another Cochrane review²⁵⁵ of several trials (1,369 women with eclampsia) compared the effectiveness of magnesium sulphate and diazepam. It demonstrated magnesium sulphate was superior to diazepam in reducing the risk of maternal death (RR 0.59, 95% CI 0.38–0.92) and the recurrence of seizures (seven trials, 1,390 women; RR 0.43; 95% CI 0.33–0.55) (see Magnesium sulphate evidence profile table 7). Similar findings on the effectiveness of magnesium sulphate compared with diazepam came from a systematic review of two studies among postpartum women.²⁵⁶

The Cochrane review found no clear differences in other measures of maternal morbidity (RR 0.88, 95% CI 0.64–1.19) or perinatal mortality (RR 1.04, 95% CI 0.81–1.34)²⁵⁵ (see Magnesium sulphate evidence profile table 7). Another finding is that magnesium sulphate is superior to phenytoin in reducing the risk of eclampsia²⁵⁴ (see Magnesium sulphate evidence profile table 6).

Effect of severity and timing in preventing eclampsia

Evidence from the Cochrane review²⁵² demonstrated similar degrees of risk reduction regardless of severity of pre-eclampsia. Among the women with severe pre-eclampsia, risk reduction was –0.02 (95% CI –0.03 to –0.01); for the non-severe pre-eclampsia group, it was –0.01 (95% CI –0.01 to 0.00) (see Magnesium sulphate evidence profile 1).

A systematic review of published reports showed that a significant number of eclamptic women had either normal blood pressure or mild-to-moderate hypertension immediately before seizure, further suggesting its benefit for prevention irrespective of the severity of pre-eclampsia²⁵⁷ (see Magnesium sulphate other evidence table). The evidence from the Cochrane review also indicated that the effect of magnesium sulphate was consistent in treating and preventing eclampsia before or after 34 weeks' gestation. However, the effect was more pronounced among women at 34 weeks or later gestation (RR 0.37, 95% CI 0.24–0.59)²⁵² (see Magnesium sulphate evidence profile 1). A small cohort study observed that pregnancy is significantly prolonged when women with severe pre-eclampsia receive magnesium sulphate for a longer period (over 48 hours), managed with an expectant protocol (9.2 ± 7.9 vs 16.6 ± 9.3 days, log-rank test, $p = 0.021$). Its findings were similar in women with severe pre-eclampsia occurring before 28 weeks' gestation ($n = 11$, 4.5 ± 5.2 vs 13.2 ± 6.8 days, log-rank test, $p = 0.035$). The study found no significant differences in major adverse outcomes.²⁵⁸

Regimen or route of administration

The most commonly used magnesium sulphate regimens are standard Pritchard or Zuspan regimens, based on evidence in the Pre-eclampsia Collaboration trial and used in the Magpie trial.^{259,260} These regimens administer a loading dose and then a 24-hour maintenance dose, either intravenously or intramuscularly.

A 2010 Cochrane review compared alternative regimens for magnesium sulphate in six studies (with 866 women).²⁶¹ The evidence from this review demonstrated that the outcomes were consistent regardless of the route of administration (IM route or IV route) or the maintenance dose (RR 0.39, 95% CI 0.24–0.65 in the IM group; RR 0.4, 95% CI 0.24–0.66 in the IV group) (see Magnesium sulphate evidence profile 2). It also showed no clear difference between the group with loading dose alone and the group with loading dose and maintenance therapy in terms of the risk of recurrence of convulsions (RR 1.13, 95% CI 0.42–3.05) or stillbirth (RR 1.13, 95% CI 0.66–1.92), and the confidence intervals are wide²⁶¹ (see Magnesium sulphate evidence profile 3).

Three trials in another review compared short maintenance regimens continuing for 24 hours after the birth (398 women). Even taken together, the evidence from these trials was insufficient to draw any reliable conclusions.²⁶¹ Other small RCTs comparing shorter durations (4 hours, 6 hours and 12 hours)^{262,263,264} of magnesium maintenance therapy postpartum with the standard 24-hour therapy

have shown similar results to the Cochrane review, but the power of these trials is also inadequate to draw conclusions that can guide clinical practice (see Magnesium sulphate other evidence table). In the systematic review of non RCT design studies, two studies (146 women) compared loading dose only with maintenance dose regimens and found no differences in seizure rates (OR 0.99, 95% CI 0.22–4.50)²⁶⁵ (see Magnesium sulphate evidence profile 5). However, the quality of the evidence is low in these studies and further high-quality studies are needed to establish the effectiveness of lower-dose regimens.

Effect of dose

One trial compared a low-dose maintenance regimen (2.5 g IM every 4 hours for 24 hours) with a standard-dose regimen (4 g IM every 4 hours for 24 hours) but the trial was too small (50 women) for drawing any reliable conclusions about the comparative effects.

A systematic review of non-RCT design studies (quasi-RCTs, cohort, case-control and cross-sectional studies) compared magnesium sulphate regimens. It showed that lower-dose regimens were as good as standard regimens in terms of preventing seizures (OR 1.02, 95% CI 0.46–2.28; 899 women, four studies)²⁶⁵ (see Magnesium sulphate evidence profile 4).

Adverse effects and safety

The Cochrane review²⁵⁴ demonstrated that the reported side effects were significantly more common among women treated with magnesium sulphate compared with a placebo group (RR 5.26, 95% CI 4.59–6.03). The most commonly reported side effects were flushing and problems at the injection site (see Magnesium sulphate evidence profile).

A cohort study demonstrated that neonatal intensive care admissions were higher among those fetuses exposed to antenatal magnesium sulphate therapy compared with those who were not (22% vs 12%, $p < 0.001$). However, the difference in length of stay in a neonatal intensive care unit was not significant (median 5 (range 2–91) vs 6 (range 3–15), $p = 0.5$).²⁵⁷

Although the Cochrane review demonstrated that toxicity as shown by respiratory depression and absent tendon reflexes was not statistically significant (RR 5.96, 95% CI 0.72–49.40),²⁵⁴ these effects may still have clinical significance (see Magnesium sulphate evidence profile). Researchers recommend clinical monitoring of tendon reflexes, respiration rate and urine output when administering magnesium sulphate, but do not advise monitoring serum magnesium levels unless the woman has an underlying condition that may be affected.²⁶⁶ The literature does not explore the impact of frequency of monitoring these signs, while studies seem to apply it somewhat arbitrary.

Because of the rare possibility of toxicity, you should only administer the magnesium sulphate maintenance dose in settings where one-on-one care, close monitoring and resuscitation/reversal medications (calcium gluconate) are available. You should also closely monitor fluid balance, signs of toxicity/maternal cardiovascular compromise and ongoing seizure activity, which may require additional treatment or support further investigations into the cause (eg, epilepsy). This guideline suggests that an IM loading dose of magnesium sulphate before transfer to a referral facility may be beneficial for women with severe disease²⁶⁷ and for women where IV access could be difficult to obtain.

Numbers needed to treat

From the Cochrane review²⁵⁴ and particularly the Magpie trial,²⁶⁰ 90 women were the NNT with magnesium sulphate to prevent one woman from having a seizure in the international population. However, in New Zealand, a country with a high gross national income, the NNT is 324.²⁶⁸ In terms of

harm (NNTH) for the mother, 1 in 200 were harmed through respiratory depression and 1 in 37 through caesarean section. For the child, none was harmed (in terms of death or neurologic disability). The Magpie trial was specifically conducted in a wide range of clinical settings in both rich and poor countries, with the aim that the results would be generalisable.

Note: Magnesium sulphate is also used for neuroprotection of the premature neonate (<30 weeks), in which case is administered to the mother in the 24 hours before birth. If a woman is having magnesium sulphate for pre-eclampsia, she does not need an additional dose for neuroprotection. No New Zealand guidelines, ratified by the Ministry of Health,²⁴⁵ are available on using magnesium sulphate for fetal neuroprotection. However, health professionals often use the external Australian and New Zealand *Antenatal Magnesium Sulphate prior to Preterm Birth for Neuroprotection of the Fetus, Infant and Child: National clinical practice guidelines*.²⁶⁹ These guidelines were developed in consultation with a multidisciplinary team from Australia and New Zealand.

Other factors: cost-effectiveness and care context

- As a preventative measure, magnesium sulphate is most cost-effective when its use is restricted to women with severe pre-eclampsia.²⁶⁸ Based on the Magpie trial 2002, economic assessment showed that cost, adjusted for US dollars (2001), to prevent a single case of eclampsia is \$21,202 in high-income countries and the cost-effectiveness is improved if it is used only for women with severe pre-eclampsia.^{254,265}
- Consider the practical aspects related to rural health care setting and referral protocols when making clinical judgements on the route of magnesium sulphate administration, given that administering for maintenance through either IV or IM routes produces a similar reduction in risk. The WHO guideline suggests that women may benefit from the loading dose before being transferred to a facility that is adequately resourced,²⁶⁷ particularly if there is a significant time delay before transfer. This may be given IM (see magnesium sulphate protocol).

Evidence statement:

Timing of birth (interventionist vs expectant management)

Timing – recommendations

In deciding on the timing of birth, consider blood pressure level and its treatment, potential complications linked with the chosen mode of birth, health of the mother and fetus, other obstetric complications or co-morbidities, and the woman's preferences.

For women with chronic hypertension

- **Before 37 weeks:** Do not recommend birth unless other maternal or fetal indications support it.
Strong recommendation; moderate-quality evidence
- **After 37 weeks:** For women with low risk of adverse outcomes, consider expectant management beyond 37 weeks with increased monitoring.
Strong recommendation; moderate-quality evidence

For women with gestational hypertension

- **Before 37 weeks:** Recommend expectant management. Do not recommend birth unless other maternal or fetal indications support it. Strong recommendation; moderate quality evidence.
Strong recommendation; moderate-quality evidence
- **After 37 and before 40 weeks:** Consider birth. The woman, her LMC and the obstetric team should negotiate the timing.
Strong recommendation; moderate-quality evidence

For women with pre-eclampsia who are stable and without severe features

- **Before (eg, 36+6) 37 weeks:** Adopt an expectant approach. Do not recommend birth if no other maternal indicators (eg, premature rupture of membranes, preterm labour or vaginal bleeding, deterioration of condition) or fetal indications support it. Usually you should manage this condition with the woman as an inpatient.
Strong recommendation; moderate-quality evidence
- **After 37 (eg, 37+0) weeks:** Recommend birth. Continuing pregnancy after 37 weeks has no appreciable benefit and increases the risk of deterioration. Decide on the timing and method after discussion with the woman, her LMC and the obstetric team.
Weak recommendation; low-quality evidence

For women with severe/unstable pre-eclampsia or eclampsia

- **Peri or pre-viability:** Manage the condition in a tertiary setting in consultation with maternal fetal medicine if possible, and with careful discussion with the woman.
Strong recommendation; moderate-quality evidence
- **Before 34 weeks:** Adopt an expectant approach in a secondary or tertiary centre with resources for maternal and fetal monitoring and critical care of the mother and the baby. If indication for birth presents, administer corticosteroids for fetal lung maturation and magnesium sulphate for fetal neuroprotection (if <30 weeks).
Strong recommendation; moderate-quality evidence

- After 34 weeks: Recommend birth after stabilising the woman in a centre with appropriate resources to care for the mother and the baby.

Strong recommendation; low-quality evidence

For women with HELLP

- Any gestational age: Recommend birth after stabilising the woman and after she has completed a course of corticosteroids ($\leq 34+6$ weeks) and magnesium for neuroprotection (if <30 weeks) (if time permits).

Strong recommendation; moderate-quality evidence

Introduction

Given that the only cure for pre-eclampsia is birth of the baby and the placenta, some clinicians follow a policy of early birth within 24 to 48 hours (interventionist management). Others prefer to delay birth until it is no longer possible to safely stabilise the woman's condition (expectant management) with the aim of improving the outcomes for the fetus.

The evidence on the effectiveness of interventionist management compared with expectant management is limited. Some of the evidence available comes from the HYPITAT trial (an RCT of 756 women at 36–41 weeks' gestation) and HYPITAT-II trial (an RCT of 703 women at 34–37 weeks' gestation). These two trials compared induction (or delivery within 24 hours if induction was contraindicated) with expectant monitoring in women with non-severe hypertensive disorders in pregnancy. A Cochrane systematic review of four RCTs of 425 women at 24–34 weeks' gestation and the MEXPRES Latin study (a RCT of 267 women 28–33 weeks with severe hypertensive disorders)^{270,271,272,273,274} were other key sources of evidence. Additional sources the GDT identified were a systematic review that included observational studies (39 cohorts, 4,650 women at <34 weeks' gestation),²⁷⁵ studies looking at outcomes beyond 39 weeks and cost analysis,^{276,277} and a study specifically addressing chronic hypertension and timing²⁷⁸ (see Timing other evidence table).

Gestational hypertension and pre-eclampsia without severe features

The evidence from the HYPITAT trial (studying women at 36–41 weeks' gestation) indicated that induced labour after 37 weeks' gestation in women with non-severe hypertensive disorders in pregnancy²⁷³ was associated with a reduced risk of severe hypertension or HELLP syndrome. The composite adverse maternal outcome in the HYPITAT trial was significantly less frequent in women who were randomised for induction of labour compared with women who were monitored expectantly (31% vs 44%, RR 0.71, 95% CI 0.59–0.86 $p < 0.0001$) (see Timing evidence profile 1). No cases of maternal or neonatal death, or eclampsia occurred in HYPITAT in either group, while HYPITAT-II observed two cases of eclampsia (absolute risk 0.6, 95% CI –0.6 to 2.1) but again no maternal or neonatal deaths occurred.^{273,279} Evidence from the first HYPITAT trial demonstrates the risks associated with expectant management: severe hypertension (10–15%), eclampsia (0.2–0.5%), HELLP (1–2%), abruptio placentae (0.5–2%), pulmonary oedema ($<1\%$), fetal growth restriction (10–12%) and fetal death (0.2–0.5%).²⁷⁴ HYPITAT-II found that while immediate birth might reduce the already small risk of adverse maternal outcomes (RR 0.36, 95% CI 0.12–1.11; $p = 0.069$), it significantly increases the risk of neonatal respiratory distress syndrome (RR 3.3, 95% CI 1.4–8.2; $p = 0.005$). The authors concluded that routine immediate birth did not seem justified.²⁷¹

Expectant care has few differences in its risks or benefits to the mother, compared with intervention for birth in women with gestational hypertension or pre-eclampsia from 24–37 weeks' gestation without severe hypertension and/or features of severe morbidity.²⁷⁴ Considering the risk–benefit balance between the two management plans, expert opinion favours continued monitoring and birth after 37 weeks unless fetal indications or severe maternal features occur²⁷⁴ (see Timing other evidence table).

The findings from a study of 357 women demonstrated that women with superimposed pre-eclampsia have similar neonatal outcomes but more maternal complications than women with pre-eclampsia without severe features who are expectantly managed before 37 weeks.²⁸⁰

Another study modelled maternal and neonatal outcomes for birth at 36–39 weeks. Its theoretical cohort was 100,000 women diagnosed with pre-eclampsia without severe features at 36 weeks' gestation and it used TreeAge software. The study also ran a cost analysis, balanced against outcomes. Weighing the neonatal risks of preterm birth, the ideal gestation for birth for optimal maternal and neonatal outcomes is at the time of pre-eclampsia diagnosis at 36 weeks, while also being cost-effective²⁷⁶ (see Timing other evidence table).

A recent retrospective cohort study, looking at 683 singleton pregnancies complicated by hypertension that birthed after 36 weeks, stratified outcomes by each week of gestation from 36–40 weeks. Planned birth before 37 weeks' gestation (compared with expectantly managed care) was associated with a statistically significant increase in adverse neonatal outcomes (10.0% vs 2.6%, $p = 0.04$) and a non-statistically significant increase in composite adverse maternal outcomes (0% vs 2.3%, $p = 0.40$) after 38 weeks' gestation. Planned birth beyond 39 weeks' gestation was associated with an increase in severe pre-eclampsia (0% vs 10.3%, $p = 0.001$). This study suggests birth between 37 and 39 weeks offers the best maternal and neonatal outcomes for this group.²⁸¹ One population study specifically looking at chronic hypertension also suggested timing of 38–39 weeks as optimal, weighing maternal and fetal outcomes. However, the authors suggested post term duration outcomes for this group needed larger RCT studies²⁷⁸ (see Timing other evidence table).

Severe pre-eclampsia

Overall, the Cochrane systematic review (four trials, 425 women, 24–34 weeks with severe pre-eclampsia) and the MEXPRE Latin study (267 women, 28–33 weeks with severe hypertensive disorders) demonstrate that the evidence is insufficient to draw reliable conclusions about the comparative effects on most adverse outcomes for the mother.^{270,272}

The Cochrane review found that expectant management may be associated with decreased morbidity for the baby, but the evidence was insufficient to draw conclusions on the effectiveness of either interventionist or expectant management in reducing perinatal mortality (RR 1.08, 95% CI 0.69–1.71)²⁷⁰ (see Timing evidence profile table 3). The reviewers observed that babies of women in the interventionist group were more likely to have intraventricular haemorrhage (RR 1.82, 95% CI 1.06 – 3.14) and hyaline membrane disease (RR 2.30, 95% CI 1.39–3.81) (see Timing evidence profile table 3). They also observed that the interventionist group was more likely to have a lower gestation at birth in days (average mean difference -9.91 , 95% CI -16.37 to -3.45), be admitted to neonatal intensive care (RR 1.35, 95% CI 1.16–1.58) and have a longer stay in that unit (average mean difference 11.14 days, 95% CI 1.57–20.72 days) than those in the expectant management group.²⁷⁰ Similarly, both the HYPITAT trials demonstrated that intervention in birth was associated with increased rates of admission to neonatal intensive care (RR 1.26, 95% CI 0.50–3.15 in HYPITAT trial; RR 2.0, 95% CI 1.0–3.8 in HYPITAT II)^{279,274} (see Timing evidence profile tables 1, 2). Babies of women in the interventionist group in the Cochrane review, however, were less likely to be small-for-gestational age, which was also a finding of the MEXPRE Latin study²⁷² (RR 0.30; 95% CI 0.14–0.65) (see Timing evidence profile table 3).

Evidence from a structured systematic review of observational studies of expectant and interventionist approaches to treatment shows that in women with severe pre-eclampsia at less than 34 weeks' gestation, the pregnancy was prolonged by 7–14 days.²⁷⁵ However, the pregnancy was also associated with higher rates of HELLP, which reduced the days of prolonged pregnancy (by a median of five days). The MEXPRE Latin trial (women at 28–33 weeks with severe hypertensive disorders) demonstrated that pregnancy was prolonged by 2.2 days for the interventionist group compared with 10.3 days for the expectant management group.²⁷²

When pre-eclampsia occurs at a pre- or peri-viable gestation (under 24 weeks of gestation approximately), the expert opinion favours considering birth in view of the associated high maternal morbidity rates (65–71%) and perinatal mortality rates of greater than 80%.^{282,283,284,285}

This evidence therefore suggests that an expectant approach to managing women whose severe pre-eclampsia began earlier than 34 weeks' gestation may be associated with decreased morbidity for the baby. It also provides opportunity for interventions for improving fetal outcomes such as fetal lung maturation and neuroprotection. However, this evidence is limited and further large trials are needed to confirm or refute these findings and establish if this approach is safe for the mother.

Indications for birth

The evidence is of very low quality, mainly from the HYPITAT study (women >36 weeks without severe features) and a review of observational studies among women with severe pre-eclampsia at less than 34 weeks' gestation.^{273,275} The HYPITAT trial demonstrated that indications for birth among the expectant management group were mainly for maternal indications (54%) with severe hypertension in 54% of those under expectant management. Other maternal indications included patient choice (28%), use of anticonvulsant drugs (21%), antihypertensive drugs (16%), gestation past 41 weeks, (14%), rupture of membranes for more than 48 hours (5%), HELLP (4%) and severe proteinuria (2%).²⁷³ Fetal distress was an indication for birth in 10% of women with expectant management.

The review of observational studies demonstrated that with expectant management, complications are higher for women with HELLP, but similar for women with severe pre-eclampsia compared with interventionist management. The evidence from this review indicates that, where women had HELLP syndrome, expectant management was harmful, with a 6.3% incidence of maternal death and an increased risk of placental abruption.²⁷⁵ A systematic review also showed that corticosteroids do not improve mortality outcomes for HELLP (RR 0.95, 95% CI 0.28–3.21)²⁸⁶ (see Timing evidence profile table 4). Among those under expectant management, birth is indicated mainly for fetal reasons (median of 70.8%, interquartile range (IQR) 53.9, 89 for those with HELLP; median 35.7%, IQR 19.6, 59.5, for those with severe pre-eclampsia)²⁷⁵ (see Timing evidence profile tables 5 and 6). With the limitations in the evidence, expert opinion supports delivering the baby where severe maternal features are present. Expert opinion also cautions that it is important to stabilise the woman before birth.

The evidence^{274,244} suggests the maternal indications for birth are: severe hypertension (refractory to treatment), HELLP, eclampsia, preterm labour or rupture of membranes, and vaginal bleeding. Fetal indications include: growth restriction/oligohydramnios, variable or late decelerations, absent or reverse umbilical artery diastolic flow, biophysical profile <6²⁷⁴ or issues with short-term variability on CTG.²⁴³ These indications depend on the gestational age. Expert opinions from recent guidelines on managing hypertensive disorders in pregnancy are consistent with this evidence on indications.^{31,32,36}

Small for gestational age

Several studies have looked at determining the best gestational age for birth when the pregnancy is complicated by a hypertensive disorder and an SGA baby. All studies identified were retrospective cohort studies and suggested that normal SGA protocols could be followed. The outcomes of a baby diagnosed as SGA did not change if their mother had hypertension; instead they were more closely related to gestational age at birth and size of the baby.^{283, 287,288}

Fetal protection

The evidence from a Cochrane review of 21 studies (3,885 women and 4,269 infants) supports using a single course of antenatal corticosteroids to accelerate fetal lung maturation where women are at risk of preterm birth.²⁸⁹ Offer repeat doses of steroids if the risk of preterm birth is ongoing.²⁹⁰ The Cochrane review demonstrated that treatment with antenatal corticosteroids is associated with an

overall reduction in fetal neonatal death (RR 0.77, 95% CI 0.67–0.89) and in severe fetal outcomes such as respiratory distress syndrome (RR 0.66, 95% CI 0.59–0.73), cerebroventricular haemorrhage (RR 0.54, 95% CI 0.43–0.69), necrotising enterocolitis (RR 0.46, 95% CI 0.29–0.74) and systemic infections in the first 48 hours of life (RR 0.56, 95% CI 0.38–0.85)²⁸⁹ (see Timing evidence profile table 7). However, evidence is lacking on the optimal dose to birth interval, the optimal corticosteroid to use, effects in multiple pregnancies, and the long-term effects into adulthood.

In line with the available evidence, the Australian and New Zealand clinical practice guideline suggests that steroids have good effect for preterm birth when gestational age is 34 weeks and 6 days or less. It also recommends a single course of antenatal corticosteroids for women with diabetes in pregnancy or gestational diabetes at risk of preterm birth (<37 weeks).²⁶⁹

Another Cochrane review of five trials (6,145 babies) demonstrated that giving women at risk of preterm birth antenatal magnesium sulphate therapy at less than 30 weeks' gestation substantially reduced the risk of cerebral palsy in their child (RR 0.71, 95% CI 0.55–0.91) and also reduced substantial gross motor dysfunction (RR 0.61, 95% CI 0.44–0.85)²⁹¹ (see Timing evidence profile table 8). The evidence from this review showed that the number of women needed to be treated for one baby to avoid cerebral palsy was 63 (95% CI 43–155). The results, however, did not show any significant effect on paediatric mortality, nor on other neurological impairments or disabilities in the first few years of life (RR 1.01, 95% CI, 0.86–1.19) (see Timing evidence profile table 8).

Beyond 39 weeks

A maternal and fetal outcomes study compared 126 women who had gestational hypertension after 24 weeks but no other co-morbidities and 564 women with uncomplicated pregnancies. It showed that neonatal outcomes were better or almost the same in the complicated pregnancies as in unaffected pregnancies, if the time of birth was between 37 and 38+6 gestational weeks (Apgar at 1 minute, $p = 0.244$; Apgar at 5 minutes, $p = 0.527$) but significantly worse at 39–41 weeks (Apgar at 1 minute, $p = 0.005$; Apgar at 5 minutes, $p = 0.033$). Gestational hypertension did not affect the mode of birth in favour of caesarean section.²⁷⁷

Another study included 683 women with hypertension at 36 weeks.²⁸¹ Before 38 weeks, planned birth was associated with a non-statistically significant increase in the primary composite adverse neonatal outcome; after 38 weeks, expectant management was associated with a non-statistically significant increase in the primary composite outcome. Expectant management beyond 39 weeks was associated with a statistically significant increase in severe pre-eclampsia ($p < 0.001$) and an infant stay in hospital of more than five days ($p = 0.05$).²⁸¹

Evidence statement:

Anaesthetic considerations

Anaesthesia – recommendations

- It is possible to use neuraxial methods of analgesia (ie, spinal, epidural and combined spinal and epidural anaesthesia (CSE)) in labour safely, even for women with lower platelet counts. However, this guideline does not generally recommend using them when the platelet count is $<80 \times 10^9/L$.
Strong recommendation; low-quality evidence
- Fluid preloading is not required when siting neuraxial anaesthetics.
Strong recommendation; very low-quality evidence
- Spinal anaesthesia and CSE are the preferred techniques for caesarean section birth if an epidural is not already in place.
Strong recommendation; very low-quality evidence
- If general anaesthesia is necessary, rapid sequence induction is the preferred technique. Aggressively prevent the hypertensive response to intubation.
Strong recommendation; low-quality evidence
- Propofol is safe and effective as an induction agent for general anaesthesia.
Weak recommendation; very-low-quality evidence
- Central venous pressure monitoring is not usually required and may be harmful.
Strong recommendation; very low-quality evidence
- This guideline does not recommend pulmonary artery catheterisation.
Strong recommendation; very low-quality evidence
- A peripheral arterial line is not required in pre-eclampsia but can be useful for monitoring blood pressure.
Strong recommendation; very low-quality evidence
- Magnesium sulphate can continue during caesarean section.
Strong recommendation; low-quality evidence
- Fluid restriction is advisable to reduce the risk of fluid overload in the intrapartum and postpartum periods. Pulmonary oedema has been a significant cause of maternal death in eclampsia/pre-eclampsia, often associated with excess fluid administration. Usually limit total fluids to 80–85 mL/hour for severe pre-eclampsia.
Strong recommendation; low-quality evidence

Introduction

Epidural analgesia lowers blood pressure and may be a useful adjunct in treating a labouring woman with pre-eclampsia. It is possible to provide surgical anaesthesia by epidural top-up, by spinal anaesthesia or by rapid-sequence induction of general anaesthesia.²⁹² Clinical practice recommendations stress that with each method, it is necessary to specifically consider its risk–benefit balance and its particular contraindications.^{293,294,295}

General anaesthesia vs neuraxial techniques

Neuraxial anaesthesia is the preferred technique for pregnant women, including those with hypertensive disorders.²⁹⁶ Part of this support comes from the findings from some observational studies that maternal risk increases with general anaesthesia,^{297,298} although the evidence is of low quality and inadequate to draw conclusions from for clinical practice.

A retrospective study (of 533 women with eclampsia) that compared general with epidural anaesthesia showed that there were no major complications with either general or epidural anaesthesia. However, epidural anaesthesia was associated with higher one-minute Apgar scores.²⁹⁹ Another study that compared general with spinal anaesthesia demonstrated better haemodynamic stability with spinal anaesthesia during caesarean section in women with severe pre-eclampsia.³⁰⁰ With no evidence available on anaesthesia modalities in women with altered consciousness, the current opinion is to be cautious in women who have had eclamptic fits and, if signs or symptoms of cerebral oedema appear, regional anaesthesia is not recommended.²⁹² Specific indications for general anaesthesia for caesarean section include coagulopathy and pulmonary oedema.²⁹²

The major disadvantages of general anaesthesia in pre-eclamptic women are the hypertensive response to intubation and the presence of laryngeal oedema,²⁹² which contributes to an increased rate of difficult and failed intubation in obstetrics. The findings from an observational study (of 38 women) showed that during general anaesthesia, an additional intravenous bolus of magnesium sulphate 40 mg/kg was effective in obtunding the response to tracheal intubation.³⁰¹ A dose-response study found a significantly improved effect on the hypertensive response to tracheal intubation in severely pre-eclamptic women undergoing caesarean section under general anaesthesia when the magnesium bolus was used in conjunction with remifentanyl at 1.34 µg/kg.³⁰² In women with severe pre-eclampsia, consider placing an arterial line before induction.

Providing general anaesthesia

The traditional technique for induction of general anaesthesia in pregnant women is to use the rapid sequence induction with thiopental and suxamethonium. While guidelines continue to recommend rapid sequence induction (with pre-oxygenation and cricoid pressure) to prevent aspiration of gastric contents at induction, there is now much wider scope to use different agents. Propofol has wide acceptance as being safe in caesarean section. The combination of rocuronium and sugammadex offers an alternative to the traditional suxamethonium for muscle relaxation. Most importantly, however, is that laryngoscopy and intubation are likely to lead to a sympathetic response. This can create a hypertensive surge that can be harmful for the woman. You should therefore anticipate such a response and treat it in advance.³⁰³ A bolus of remifentanyl (1–1.5 µg/kg)³⁰² is effective in obtunding the sympathetic response to laryngoscopy, and has a very short duration of action in the newborn. If you use opioids to obtund the sympathetic response, inform the neonatal team so that it can prepare for neonatal narcosis. Propofol may suppress the hypertensive response to intubation more effectively than thiopental.³⁰⁴ Other drugs, including Alfentanil, labetalol and/or magnesium, may also be added. Anaesthetists should also be aware of a hypertensive response at extubation and take steps to prevent it.^{305,306}

Pregnant women in general are more difficult to intubate than their non-pregnant counterparts. Women with pre-eclampsia may have airway oedema, which makes intubating them even more difficult than other pregnant women. A strategy for general anaesthesia should include a backup plan for airway management if a failed intubation occurs.³⁰⁷

General anaesthesia for caesarean section is associated with an increased risk of awareness³⁰⁸ so you should consider depth of anaesthesia monitoring. Volatile anaesthetic agents relax the myometrium and can increase bleeding. Avoid NSAIDs. Anaesthetists should also observe the fluid restrictions recommended in these guidelines and provide thromboembolic prophylaxis postoperatively.

Magnesium sulphate

The evidence also shows that magnesium sulphate infusion is safe in the setting of regional anaesthesia (haemodynamic stability and coagulation) and general anaesthesia (control of intubation response).²⁹⁵ Researchers have suggested that magnesium reduces catecholamine release and thus

allows better control of the adrenergic response during intubation and decreases the frequency of convulsive seizures in pre-eclampsia and their recurrence in eclampsia.³⁰⁹

Regional anaesthesia

A prospective study (of 100 women) compared the haemodynamic effects of spinal and epidural anaesthesia for caesarean section in severely pre-eclamptic women. It demonstrated a significant difference in the mean arterial pressure, with more women in the spinal group exhibiting hypotension ($p < 0.001$).³¹⁰ The findings also showed, however, that the duration of significant hypotension (systolic arterial pressure <100 mmHg) was short (<1 min) in both groups. The researchers observed that treatment involved use of more ephedrine in the spinal group than in the epidural group (median 6 vs 0 mg) but hypotension was easily treated in all women. Neonatal outcomes were of similar in both groups.³¹⁰

Another prospective cohort study showed that in comparison with healthy term pregnant women, women with severe pre-eclampsia had a less frequent incidence of spinal hypotension, which was less severe and required less ephedrine.^{311,312} Because of these effects, regional anaesthesia also may provide additional control of hypertension if other methods are not proving effective in labour. Take care to monitor for hypotension, particularly if the woman is on antihypertensive drugs.

Although the quality of evidence is inadequate to determine whether spinal or epidural anaesthesia is superior, the current expert opinion supports using spinal anaesthesia for caesarean section in pre-eclampsia, though epidural and CSE are not contraindicated. Using similar doses to those for healthy pregnant women is appropriate, if there are no contraindications to regional anaesthesia, and if an epidural catheter has not been placed for labour analgesia.^{295,313} Given the current evidence and clinical practice in some settings, this guideline encourages placing an epidural catheter early in women going into labour, because it secures a means of delivering regional anaesthesia (and avoiding the risks of general anaesthesia) if an emergency caesarean section is then required.³¹³

Low platelet count

No reliable evidence is available on the lowest permissible platelet count for regional anaesthesia in pre-eclampsia.³¹⁴ Platelet counts may fall rapidly in pre-eclampsia, so a recent count (within six hours) is required. In a cohort study (of 606 women) that assessed changes in coagulation using thromboelastography, the evidence showed that severe pre-eclamptic women with a platelet count $<100 \times 10^9/L$ were significantly hypocoagulable with an amplitude <54 mm (the lower limit of maximum amplitude in healthy pregnant women enrolled in this study) when compared with healthy pregnant women and other pre-eclamptic women.³¹⁵ In addition, a study of 80 women demonstrated that 30 had an epidural anaesthetic placed when the platelet count was $<100 \times 10^9/L$ (range 69–98 $\times 10^9/L$), 22 had an epidural anaesthetic placed with a platelet count $>100 \times 10^9/L$ that subsequently decreased below $100 \times 10^9/L$. The study found no neurological complications.³¹⁶

These studies were small and probably lack the power to make conclusions around safe platelet levels. Based on the current evidence, expert opinion favours performing spinal anaesthesia if the platelet count exceeds 75–80 in severe pre-eclampsia and individual assessment of the patient supports it.^{293,295,314} Anaesthetists should also be aware that other abnormalities of coagulation may co-exist and that they should interpret platelet counts in the context of other tests of coagulation, including dynamic ones such as thromboelastography. In a patient with a very low platelet count, neuraxial anaesthesia may still be preferable if the anaesthetist considers the risks of general anaesthesia are still greater.³¹⁷

Fluid management

It is essential to consider fluid management when making decisions about anaesthesia for pregnant women with hypertension because IV fluid boluses have a transient impact on central venous pressure and pre-eclamptic women are more susceptible to pulmonary oedema.³¹³ Although preloading with intravenous fluids before traditional high-dose local anaesthetic blocks may have some benefits for the fetus and mother when the woman is healthy, no evidence specific to pregnant women with hypertensive disorders is available.

A Cochrane review of six studies (473 healthy pregnant women) indicated low-dose epidural and CSE analgesia techniques may reduce the need for preloading.³¹⁸ However, the studies were too small to draw conclusions to guide clinical practice and specifically the management of labour in hypertensive pregnant women.

Central venous lines and pulmonary artery catheters

In pre-eclampsia complicated by pulmonary oedema, or oliguria that persists despite limited plasma volume expansion, circulatory parameters are diverse enough to suggest a role for central venous lines and pulmonary artery catheters in guiding therapy. However, there is no evidence that placing a central venous catheter to determine central venous pressure has any benefit and central venous pressure correlates poorly with pulmonary wedge pressure.³¹⁹ Furthermore, evidence from a retrospective study showed a high incidence of infection among women who received central venous catheters.³²⁰

Using pulmonary artery catheters to assess left ventricular preload has shown poor outcomes in pre-eclamptic women. Because the approach is associated with a significant incidence of complications, the focus has moved to non-invasive technologies.^{293,294} However, the GDT found no randomised controlled clinical trials showing that pulmonary artery catheters are clinically more useful than echocardiographic techniques in hypertensive pregnancy.³¹⁹ Although non-invasive methods for determining cardiac output have significant drawbacks, support is increasing for non-invasive haemodynamic monitoring techniques in clinical practice in view of the risk associated with invasive monitoring.³²¹

Evidence statement: Mode of birth

Mode of birth – recommendations

- The preferred mode of birth is always vaginal unless it is contraindicated for the mother or the fetus. Eclampsia is not an indication for caesarean section. In many cases induced labour is a safe option.
Weak recommendation; low-quality evidence
- Vaginal birth is often possible in women with pre-eclampsia or eclampsia. Evidence shows neonatal outcomes are better even if an induction ends in caesarean than for elective caesarean at many gestations.
Strong recommendation; moderate-quality evidence
- Make the decision about mode of birth with the woman and the medical team (including obstetrics, neonatology and anaesthetics).
Weak recommendation; very low-quality evidence
 - Make vaginal birth with or without induction the preferred choice in women with pre-eclampsia but no other obstetric contraindications.
 - Before 28 weeks of gestation, however, labour induction is less successful and maternal and fetal disease is likely to be more severe. Consider caesarean section for this reason.
- Actively managing the third stage of labour is clinically indicated in women with hypertensive disorders in pregnancy.
Strong recommendation; very low-quality evidence
- Avoid ergometrine and Syntometrine® as an uterotonic in women with hypertensive disorders except when massive obstetric haemorrhage occurs.
Weak recommendation; very low-quality evidence

Introduction

After deciding and agreeing on intervention to end the pregnancy (as discussed in the Timing evidence profile), you need to consider the mode of birth. The primary consideration is the urgency of birth of the baby for the mother's benefit.

Induction vs elective caesarean section

When assessing a woman with hypertension or pre-eclampsia for induction or caesarean section, base the decision on best evidence, the clinical picture, local guidelines and the woman's preferences. The current evidence focuses mainly on severe pre-eclampsia. It comes from the outcomes of the HYPITAT²⁷³ and HYPITAT-II²⁷⁹ randomised control trials and a number of smaller, low-quality studies.

Does a caesarean section cause benefit or harm?

A small retrospective chart review study asked whether caesarean section had any benefit at all, for mother or baby, if it was not absolutely necessary.³²² Of 93 women (who had the option of induction), 34 had an immediate caesarean section and 59 had induced labour. Of those who had induced labour, 63% delivered vaginally and 37% underwent caesarean section. Pulmonary complications in the mother and neonate were more common in caesarean section ($p < 0.05$). Caesarean section also did not reduce any morbidity. Bishop score did not affect the labour induction success rate. The researchers concluded that when caesarean section was an option, immediate caesarean section provided no benefit to patients with severe pre-eclampsia³²² (see Mode of birth other evidence table).

A prospective cohort study of 500 pregnant women with severe pre-eclampsia found labour was spontaneous in 22.0% and induced in 28.2%, while 49.8% had an elective caesarean section. Ninety-five (67.4%) of the patients experiencing induced labour delivered vaginally.³²³ Total caesarean rate was 68.2%. The risk of severe maternal morbidity was significantly greater in patients who had a caesarean section (54.0% vs 32.7%), whether or not they were in labour. Factors that continued to be associated with severe maternal morbidity following multivariate analysis were a diagnosis of HELLP syndrome after birth (OR 3.73, 95% CI 1.55–9.88) and having a caesarean (OR 1.91, 95% CI 1.52–4.57) (see Mode of birth evidence profile 4).

Pacher's³²⁴ retrospective study focused on 130 cases of women with pre-eclampsia who delivered via elective or emergency caesarean (37–41 weeks' gestation). It found the Apgar score was significantly higher in the pre-eclamptic women who had an emergency caesarean section compared with those who had an elective one (5 mins: elective = 9.61 vs emergency = 9.88, $p = 0.020$; 10 mins elective = 9.88 vs emergency = 10.00, $p = 0.001$).³²⁴

Does induction cause benefits or harm?

Evidence from both HYPITAT (36–41 weeks' gestation) and HYPITAT-II (34–37 weeks) found that induction was not associated with higher rates of caesarean section in women with hypertensive disorders in pregnancy (RR 0.75, 95% CI 0.55–1.04 and RR 0.94, 95% CI 0.75–1.16, respectively) compared with expectant management^{273, 279} (see Mode of birth evidence profiles 1 and 2). In HYPITAT, composite adverse maternal outcomes were significantly better in the induction group (RR 0.71, 95% CI 0.59–0.86). However, HYPITAT-II showed no significant difference in maternal outcomes between birth groups. Also in HYPITAT-II, composite neonatal adverse outcomes were worse in the immediate birth group, with respiratory distress syndrome diagnosed in 5.7% of the neonates compared with 1.7% in the expectant monitoring group (RR 3.3, 95% CI 1.4–8.2; $p = 0.005$).²⁷⁹ HYPITAT found no significant difference in this area (see Mode of birth evidence profiles 1 and 2).

Two retrospective studies queried whether induced labour was harmful when compared with caesarean section without labour, in the birth of very low birthweight infants (at earlier gestations), and where pregnancies were complicated by severe pre-eclampsia.^{325,326} Among the women with severe pre-eclampsia who delivered infants weighing between 750 and 1,500 g, 52% of 278 women (study 1) and 70% of 400 women (study 2) had labour induced and 48% (study 1) and 30% (study 2) delivered by caesarean without labour. In the induced group, 50 women (34% in study 1) and 182 women (65% in study 2) delivered vaginally. Apgar scores of 3 or less at five minutes were more likely in the induced-labour group (6% vs 2%, $p = 0.04$, study 1; 6% vs 3%, $p = 0.04$, study 2). However, other neonatal outcomes, including respiratory distress syndrome, grade 3 or 4 intraventricular haemorrhage, sepsis, seizures and neonatal death, were similar in the two groups, in both studies^{325,326} (see Mode of birth other evidence table).

A post-hoc study looked at a subsample of women with pregnancy-induced hypertension or mild pre-eclampsia at term, who had participated in the randomised HYPITAT trial. It assessed them for cardiovascular risk factors 2.5 years after they had given birth, comparing them in two cohorts: induction of labour ($n = 110$) and expectant monitoring ($n = 91$). Evidence showed that induction of labour does not affect the clinical and biochemical cardiovascular profile at 2.5 years postpartum.³²⁷

Induction outcomes

One study examined the success rate and analysed differences in neonatal outcomes with induction, compared with elective caesarean section in women with early-onset severe pre-eclampsia.³²⁸ Vaginal birth occurred in 6.7% of women induced between 24 and 28 weeks' gestation, 47.5% of those induced between 28 and 32 weeks, and 68.8% of those induced between 32 and 34 weeks.³²⁸ Success of induction was significantly and positively associated with increasing gestational age (AOR 1.43, 95% CI 1.24–1.66), while it was negatively associated with nulliparity (AOR 0.21, 95% CI 0.11–0.42) and

previous caesarean section (AOR 0.09, 95% CI 0.02–0.40). Individual or composite neonatal outcomes did not differ between women who were induced and those having an elective caesarean section, except for bronchopulmonary dysplasia (9.2% vs 33.0% respectively, AOR 0.48, 95% CI 0.24 – 0.97) (see Mode of birth other evidence table).

Induced labour in pre-eclamptic women has a higher risk of failure (8.2% vs 1.7%, OR 5.06, 95% CI 1.97–13.28), and consequently, a higher rate of caesarean section (28% vs 16%, OR 2.09, 95% CI 1.36 – 3.18) than in women who are not pre-eclamptic. When controlled by logistic regression for Bishop score, parity, method of induction, epidural analgesia, macrosomia, and gestational age, the pre-eclamptic group's risk of failed induction was four times higher and its risk of caesarean section was twice as high.³²⁹ Kim et al's retrospective cohort study of 3,505 women³³⁰ found that those with pre-eclampsia who were induced, had higher caesarean section rates compared with those without it, regardless of parity or gestational age (AOR 1.90, 95% CI 1.45–2.48). However, most women with pre-eclampsia still had successful vaginal deliveries.

The success of induction rates varies between studies from 6.7% to more than 60%, appearing to correlate with week of gestation.²⁷¹ However, because the data suggests that neonatal outcomes are better in emergency caesarean sections than elective ones,^{324,325} encourage women with pre-eclampsia and no contraindications to consider induction as an option.

Influences on success of induction

One retrospective study aimed to determine the rate of vaginal birth after labour induction in women with severe pre-eclampsia separately from term and potential predictors of success. For this purpose, it reviewed selected charts of 306 women with singleton pregnancies complicated by severe pre-eclampsia who delivered at 24–34 weeks' gestation.³³¹ Bishop score was a statistically significant predictor of successful induction (OR 1.38, 95% CI 1.11–1.71, $p = 0.003$), with a higher score in the vaginal birth after induction group than in the caesarean section after induction group. However, the two groups did not differ significantly in their use of cervical ripening agents, gestational age at birth, birthweight, Apgar score at five minutes or postpartum endometritis³³¹ (see Mode of birth other evidence table).

A post-hoc analysis of data from the HYPITAT trial found that some factors were independent antenatal and intrapartum predictors that a pregnancy complicated by hypertension would end in caesarean section.³³² Of the 756 women who were included, 126 (17%) delivered by caesarean section. In multivariable analysis, parity, non-Caucasian ethnicity, previous abortion, creatinine, proteinuria as well as the cervical components, such as cervical length, engagement and dilatation were independent antepartum predictors of caesarean section. Intrapartum predictors also included gestational age at birth, use of antibiotics, progression of disease to a high-risk situation and uric acid.³³²

Researchers have looked at various other models of influences that may influence the success rate of induction, including one study that examined obesity as a predictive factor.³³³ This retrospective cohort study of 609 women suggested that among women affected by pre-eclampsia, obesity complicates labour induction. It increases the risk of caesarean section; even small increases (5 units) in BMI were associated with a 16% increased odds of caesarean birth.

Another small prospective study in Japan³³⁴ aimed to reduce the caesarean rate in pre-eclamptic women. It found that the introduction of specific indicative criteria for caesarean section was associated with a significant reduction in the caesarean section rate, from 95% (43 of 45) to 41% (17 of 41). These criteria involved: occurrence of warning signs or symptoms of serious complication (including significant change in blood pressure); uncontrollable rises in blood pressure; and ineffective labour induction (measured against a set definition of progress).

Methods of induction

The methods of induction of labour in clinical practice include administering pharmaceutical agents (such as oxytocin, prostaglandin E2 or misoprostol) and mechanical methods. This section presents the evidence around the implications of these methods as applied to women with pre-eclampsia.

The evidence from a post-hoc analysis of the HYPITAT trial data showed that induced labour, when indicated in women with gestational hypertension or mild pre-eclampsia, and with an unfavourable cervix (long cervix >40 mm or a low Bishop score 5 or less), helped to reduce the caesarean section rate (compared with the rate for those with a favourable cervix).³³⁵ A Cochrane review used two studies (n = 234) to compare Bishop score with transvaginal ultrasound (TVUS) to assess pre-induction cervical ripening in women admitted for induction of labour. The findings did not show any clear difference between the Bishop score and TVUS groups for vaginal birth (RR 1.07, 95% CI 0.92–1.25) or caesarean section (RR 0.81, 95% CI 0.49–1.34)³³⁶ (see Mode of birth evidence profile 3).

Evidence around the effectiveness of different methods of induction specific to pregnant women with hypertension is inconclusive. A prospective randomised trial (of 45 women) with established pre-eclampsia and unripe cervix (Bishop scores ≤5) demonstrated that prostaglandin E2 (PGE2) was safe in pre-eclamptic women.³³⁷ In this trial, 29.1% of women treated with PGE2 (0.5 mg intracervical) went into labour without any further induction procedure, and in 62.6% the cervix ripened so much that labour could be induced by amniotomy and/or oxytocin infusion compared with the control/placebo group. In the placebo group the corresponding figures were 4.8% (p < 0.05) and 66.7% (0.5 mg intracervical PGE2). The result also showed that the time interval from the first gel to labour induction or augmentation in the PGE2 group (13.8 ± 9.4 hours) was significantly shorter (p < 0.05) than that in the placebo group (19.0 ± 9.3 hours), as was also the time interval from the first gel to the birth (23.0 ± 17.6 hours vs 33.6 ± 23.1 hours). The study found no uterine hypertonus or fetal bradycardia and no adverse neonatal outcome in either group.³³⁷

Third stage management

Any induction or augmentation of labour carries increased risk of postpartum haemorrhage but some research suggests that the risk for women with pre-eclampsia is higher. One study in Norway compared postpartum bleeding between women with pre-eclampsia and women without.³³⁸ Excess postpartum bleeding (>1,500 mL) occurred in 3.0% (399 of 13,166) of pre-eclampsia cases and in 1.4% (4,223 of 301,919) of women with normal blood pressure (p < 0.01). Moderate bleeding postpartum (>500 mL) was also more common in pre-eclampsia cases (22.9% vs 13.9%, p < 0.01). Similar patterns occurred irrespective of parity, and the patterns did not vary according to type of birth (caesarean section or not).³³⁸ Another study also showed a significantly increased risk of postpartum haemorrhage in term pre-eclamptics compared with those without pre-eclampsia (42.8% vs 28.7%, AOR 1.77, 95% CI 1.32–2.37).³³⁹ These findings suggest that actively managing this group in the third stage of labour is clinically indicated, even in a non-induced, spontaneous birth of a pre-eclamptic woman. Evidence about uterotonics in relation to women with hypertension is limited. However, one RCT demonstrated that carbetocin was as effective as oxytocin in preventing postpartum haemorrhage in women with severe pre-eclampsia³⁴⁰ (see Mode of birth other evidence table).

Using ergometrine or Syntometrine™ is contraindicated in hypertensive cases as ergometrine stimulates vasoconstriction, causes hypertension, and may cause headache, convulsions and even death in women with pre-eclampsia. It may also precipitate postpartum pre-eclampsia.^{341,342} However, it may be of benefit if severe haemorrhage occurs.

Evidence statement:

Long-term risks

Long-term risks – recommendations

- Give women with a history of hypertensive disorders in pregnancy information on long-term risks of pre-eclampsia, including cardiovascular disease, and the importance of following a healthy lifestyle. (See Table 6 for a list of these risks.)
Strong recommendation; very low-quality evidence.
- Give women with a history of pre-eclampsia information on risks linked with subsequent pregnancies. Give them the opportunity to discuss contraceptive options, if they wish to.
Weak recommendation; very low-quality evidence
- Assess women with a history of pre-eclampsia every year for blood pressure, lipids, blood glucose, thyroid function and BMI. Long-term risks appear to increase significantly 10 years after the initial hypertensive event. Take this timing into account when advising women on ongoing surveillance for these risks.
Weak recommendation; very low-quality evidence

Introduction

Within days of a pre-eclamptic pregnancy – 16 days on average – blood pressure usually returns to normal. However, for those who had early onset severe pre-eclampsia, it can take up to three months. In addition, a proportion of women who had pre-eclampsia will remain hypertensive and are presumed to have had previously unidentified chronic hypertension.^{343,344}

Despite their recovery to a normal blood pressure, evidence indicates that many women who have had pre-eclampsia will develop long-term complications.³⁴⁵ Large observation studies have found that women who have experienced pre-eclampsia, and especially early onset pre-eclampsia, have a much higher risk of death by stroke or cardiovascular disease than those who have not.^{343,346} Studies indicate that annual hypertension screening and treatment in primary care in women who have experienced pre-eclampsia at any gestation could be cost-effective in preventing future cardiovascular disease.^{344,347}

Future pregnancies

A woman who has had pre-eclampsia in the first pregnancy has a higher risk of gestational hypertension (RR 6.3, 95% CI 3.4–12)²⁵ and a seven times higher risk of pre-eclampsia in a second pregnancy (unadjusted RR 7.19, 95% CI 5.85–8.83 from all studies; RR 7.61, 95% CI 4.30–13.47 from case-control studies).²² Having gestational hypertension also increases the risk that a woman will experience this again (RR 3.4, 95% CI 2.0–5.8)²⁵ or pre-eclampsia (OR 7.57, 95% CI 2.31–24.78)²⁶ in a subsequent pregnancy.

Health professionals can give women advice about reducing risk factors for future pregnancies, such as by lowering BMI. However, no studies have proven that this approach will reduce the incidence when women are already at high risk. Further, they may not be able to modify some risk factors they receive education on, for example, age. A woman may wish to consider her contraceptive options in such situations.³⁴⁸

Cardiovascular disease

Studies have reported pre-eclampsia and gestational hypertension have a detrimental effect on future cardiovascular health. However, it is uncertain whether the vascular changes induced by systemic

endothelial damage manifest in later life as cardiovascular diseases (CVD) or whether the two simply share common underlying risk factors, with hypertensive disorders in pregnancy representing an earlier stage on the path to cardiovascular problems.³²

The evidence for long-term CVD is mainly based on a systematic review of 50 case-control and cohort studies, and meta-analysis of 43 studies involving over a million women in total.²⁸ The evidence from this review demonstrates that women with a history of pre-eclampsia face an approximately two times greater risk of developing CVD (OR 2.28, 95% CI 1.87–2.78) and cerebrovascular disease (OR 1.76, 95% CI 1.43–2.21), and a three times greater risk of hypertension (RR 3.13, 95% CI 2.51–3.89)²⁸ (see Risks evidence profile 1). These findings are consistent with the findings from earlier meta-analyses^{27,346,349} (see Risks other evidence tables). However, this review found no evidence to demonstrate the risk of CVD increases when pre-eclampsia is associated with preterm birth (RR 1.32, 95% CI 0.79–2.22).²⁸

Other studies show that women who had gestational hypertension were at higher risk of later developing chronic hypertension (RR 3.39, 95% CI 0.82–13.9), cardiovascular disease (RR 1.66, 95% CI 0.62–4.41)²⁷ and cerebrovascular disease (RR 1.47; 95% CI 1.05 – 2.0).²⁹

Another study showed that lifestyle interventions (exercise, dietary habits and smoking cessation) were useful in reducing long-term risk of CVD and decreasing cardiovascular risk (OR 0.91, IQR 0.87–0.96)³⁵⁰ in women with a history of pre-eclampsia. However, the cardiovascular risk factors do not fully explain the risk of CVD after pre-eclampsia, suggesting that pre-eclampsia brings an additive risk. After correction for known cardiovascular risk factors, the odds ratios of pre-eclampsia for ischaemic heart disease and for stroke are 1.89 (IQR 1.76–1.98) and 1.55 (IQR 1.40–1.71) respectively.³⁵⁰

Cancer

Evidence from other systematic reviews showed no increase in the risk of cancer in women with history of pre-eclampsia (RR for any cancer 0.96, 95% CI 0.73–1.27; RR for breast cancer 1.04, 95% CI 0.78–1.39)²⁷ (see Risks evidence profile 2).

Thyroid disease

Two prospective population-based cohort studies, the Northern Finland Birth Cohorts 1966 and 1986,³⁵¹ followed women who had pre-eclampsia (n = 955) or normal blood pressure (n = 13,531) during pregnancy to investigate who later developed hypothyroidism 20–40 years after they had given birth. Overall, pre-eclampsia in pregnancy was not significantly associated with subsequent hypothyroidism. However, late pre-eclampsia (>36 weeks) in nulliparous women was associated with a 1.8 times greater risk (95% CI 1.25–3.56) of later developing hypothyroidism (see Risks evidence profile 3).

Diabetes

Because pre-eclampsia is linked with a woman's body mass index, as well as with other features of the metabolic syndrome such as insulin resistance, hyperlipidemia, waist circumference, and waist:hip ratio, women who have had pre-eclampsia are at risk of developing type 2 diabetes mellitus in the future.

Several population studies have confirmed the incidence of type 2 diabetes increases in women who have had a pregnancy complicated by pre-eclampsia.³⁴⁵ One study from Scotland showed that women who have had pre-eclampsia have an odds ratio of 1.40 (95% CI 1.12–1.75) of developing type 2 diabetes, after correcting for confounding factors.³⁵² Another study from the United States gave a hazard ratio of 1.86 (95% CI 1.22–2.84) after pre-eclampsia, even when it is not associated with gestational diabetes.⁶

Renal disease

Researchers believe that pre-eclampsia-triggered metabolic stress may cause vascular injury, thus contributing to the development of CVD and/or chronic kidney disease (CKD) in the future.³⁵³

In one study, pre-eclampsia during the first pregnancy was associated with a relative risk of end-stage renal disease of 4.7.³⁰ A systematic review concluded that at a weighted mean of 7.1 years postpartum, women with a history of pre-eclampsia had a four times greater risk of microalbuminuria compared with women with uncomplicated pregnancies, and for women with severe pre-eclampsia the risk was eight times greater³⁵⁴ (see Risks evidence profile 5).

Cognitive effects

A suggestion is that the pathophysiology of eclampsia represents an expression of posterior reversible encephalopathy syndrome (PRES) characterised by lesions in the brain due to ischaemia and oedema affecting cognitive function in the short and long term.³⁵⁵ Research findings demonstrated that women were more likely to report impaired cognitive functioning several years after a pregnancy that was complicated by eclampsia than healthy parous women. A study of 92 women observed that formerly eclamptic women scored significantly higher on the Cognitive Failures Questionnaire than healthy parous control subjects. In addition, women who experienced multiple eclamptic seizures reported more cognitive impairment than those who had experienced one seizure³⁵⁶ (see Risks other evidence table).

Another matched case-control study (of 20 women at three to eight months postpartum) demonstrated that formerly pre-eclamptic women had significantly lower scores on most indices of the auditory-verbal memory test compared with women who had uncomplicated pregnancies.³⁵⁷ In this study, the differences in level of intellectual functioning, language tests, attention and concentration tests and executive functioning, depression and anxiety score were not significant. However, another long-term follow-up study (of 145 women) demonstrated that both pre-eclamptic and eclamptic women performed significantly worse on the motor functions domain compared with women who had uncomplicated pregnancies ($p < 0.05$). They also scored worse on the Cognitive Failures Questionnaire ($p < 0.01$) and the Hospital Anxiety and Depression Scale on both anxiety ($p < 0.01$) and depression ($p < 0.05$) subscales³⁵⁸ (see Long-term other evidence table).

Other long-term effects such as visual loss have been related to the cerebral ischaemia and lesions associated with hypertensive disorders in pregnancy. However, the current evidence suggests that the visual loss women with a history of eclampsia report is likely to be related to higher-order visual function rather than the pre-eclampsia.³⁵⁹

Effects on the baby

Looking at the effects on the children of women who experienced pre-eclampsia, a systematic review of 18 cohort and case-control studies ($n = 45,249$ individuals aged 4–30 years) demonstrated they had an increased risk of cardiovascular disease.³⁵⁰ The evidence from this review showed that in utero exposure to pre-eclampsia was associated with a 2.39 mmHg (95% CI 1.74–3.05) higher systolic and a 1.35 mmHg (95% CI 0.90–1.80) higher diastolic blood pressure during childhood and young adulthood (see Long-term evidence profile 4). The associations were similar in children and adolescents, for different genders, and with variation in birthweight, but BMI increased by 0.62 kg/m². The evidence was insufficient to identify consistent variation in lipid profile or glucose metabolism.³⁶⁰ Furthermore, review of published literature has suggested the importance of differentiating the direct effect of hypertension in pregnancy from other risk factors that may confound the observed results.³⁶¹

Research has found the children of pregnancies complicated by maternal hypertension tend to have lower neurocognitive ability, but has associated this with intrauterine growth restriction.³⁶² A study of

1,389 children (mean age 10.59, SD=0.19) drawn from the Western Australian Pregnancy Cohort (Raine Study) demonstrated that verbal ability at age 10 years was lower among children of women who had hypertension during pregnancy (pre-eclampsia or gestational hypertension) compared with children of women with normal blood pressure.³⁶³ It assessed verbal ability with the Peabody Picture Vocabulary Test – Revised (PPVT-R), and non-verbal ability with Ravens Coloured Progressive Matrices (RCPM). The results showed the mean PPVT-R score was 1.83 (95% CI –3.48 to –0.17) points lower among children from hypertensive pregnancies than from normotensive pregnancies. The evidence from this study indicates that hypertension in pregnancy is a possible risk factor for the reductions in children’s verbal ability, but the link needs further investigation (see Long-term other evidence table).

Other factors – clinical use and women’s preferences

- The present evidence on the long-term effect of pre-eclampsia is of modest quality, and its clinical use is limited.
- In educating women, health professionals need to customise the evidence they present to suit each individual woman’s abilities to interpret the limitations in evidence for the risks of long-term illnesses.
- Research has found that many women are unaware of the long-term implications of pre-eclampsia and want to know about these risks. However they are also adjusting to motherhood, so health professionals must allow them time to become fully engaged with the information.³⁶⁴
- No studies have established whether postnatal lifestyle changes will reduce long term effects for women who have experienced hypertensive disorders in pregnancy. More evidence is required in this area.

Table 6: Risk of developing long-term conditions for women who have had gestational hypertension or pre-eclampsia

Future risk	Hypertensive disorder in index pregnancy	
	Gestational hypertension*	Pre-eclampsia
	Relative risk (95%CI)	
Gestational hypertension in future pregnancy	3.4 (2.0–5.8) ²⁵	6.3 (3.4–12.0) ²⁵
Pre-eclampsia in future pregnancy	OR 7.57 (2.31–24.78) ²⁶	7.19 (5.85–8.83) ²²
Chronic hypertension	3.39 (0.82–13.9) ²⁷	3.13 (2.51–3.89) ²⁸
Cardiovascular disease	1.66 (0.62–4.41) ²⁷	2.28 (1.87–2.78) ²⁸
Cerebrovascular disease	1.47 (1.05–2.0) ²⁹	1.76 (1.43–2.21) ²⁷
Venous thromboembolism	–	1.79 (1.37–2.33) ²⁷
End-stage kidney disease	–	4.3 (3.3–5.6) ³⁰

* More research is required around the long-term effects of gestational hypertension.
CI = confidence interval.

Glossary

Adjusted odds ratio (AOR)	The odds ratio (OR) when adjusted for confounders. This means factors that may influence the specific outcome are adjusted for. For example, if you wanted to know the true incidence of the recurrence of pre-eclampsia in a subsequent pregnancy, you would want to adjust for other risk factors (smoking, BMI, diabetes) in your calculations.
Adverse event	An adverse outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it.
Antenatal	Occurring before birth; concerned with the care and treatment of the unborn child and pregnant women.
Body mass index (BMI)	The body's weight in kilograms divided by the square of the height in metres. The measurement is used to assess obesity.
Cochrane review / Cochrane systematic review	A systematic review of the evidence usually from randomised controlled trials relating to a health problem or health care intervention, produced by the Cochrane Collaboration. Available electronically as part of the Cochrane Library.
Confidence interval (CI)	A range of values for a population outcome estimated from a study. It will depend on the number of study recruits and the variation in the outcome data. A 95% CI means that if the study was repeated 100 times with a different sample of recruits and a CI calculated each time, the interval would contain the 'true' value of the population outcome 95 times. In general, larger studies have narrower confidence intervals, indicating that their results have a greater degree of accuracy.
Control group	A group of patients that receives no treatment, a treatment of known effect or a placebo (dummy treatment) as part of a study. The purpose of this group is to provide a comparison for a group receiving an experimental treatment, such as a new drug.
Eclampsia	Seizures (convulsions) in a pregnant woman related to hypertensive disorders in pregnancy.
Evidence statement	A table summarising the results of a collection of studies that together represent the evidence supporting a recommendation or series of recommendations in a guideline.

Expectant management	Continuation of the pregnancy beyond 48 hours while monitoring the mother and the fetus, rather than intervention.
Fetal	Of or relating to a fetus or to the period of its development.
Gestation	The time from conception to birth. The duration of gestation is measured from the first day of the last normal menstrual period.
Gestational age	The period of time between last menstrual period and birth.
Harms	Adverse effects
Heterogeneity	Also called 'lack of homogeneity'. The term is used in meta-analyses and systematic reviews to describe the results or estimates of effects of treatment from separate studies that seem to be very different in terms of the size of treatment effects or even to the extent that some indicate beneficial and others suggest adverse treatment effects. Such results may occur due to differences between studies in terms of the patient populations, outcome measures, definition of variables or duration of follow-up.
Homogeneity	Where the results of studies included in a systematic review or meta-analysis are similar, with no evidence of heterogeneity. Results are usually regarded as homogeneous when differences between studies could reasonably be expected to occur by chance.
Hypertension	High blood pressure.
Informed choice	When a woman has the autonomy and control to make decisions about her care after a process of information exchange that involves providing her with sufficient, evidence-based information about all options for her care, without any party coercing her or withholding information about any options.
Informed consent	When a woman consents to a recommendation about her care after a process of information exchange that involves providing her with sufficient, evidence-based information about all the options for her care so that she can make a decision, without any party coercing her.
Intrapartum	Relating to the period of labour and birth.
Multidisciplinary team	A team that may include, as relevant to the clinical circumstances, obstetrician, midwives, obstetric physician, anaesthetist and/or neonatologist/paediatrician experienced in the care of women with hypertensive disorders in pregnancy.

Neonatal	Relating to the neonatal period, which is the first four weeks after birth.
Neuraxial	Anaesthesia. Also known as regional anaesthesia. Can be spinal, epidural or combined spinal and epidural anaesthesia (CSE).
Number needed to harm (NNTH)	The number of patients who need to be treated with the new or intervention treatment (rather than the control treatment) for one patient to be harmed from the new treatment.
Number needed to treat (NNT)	The number of patients who need the new or intervention treatment (rather than the control treatment) for one patient to benefit from the new treatment.
Obstetric team	For the purposes of this guideline, the obstetric team is a specialist team that will include an obstetric specialist and registrar, but may also include obstetric physician, maternal fetal medicine specialist and/or neonatologist.
Odds ratio (OR)	Similar to risk ratio (RR) but with a different statistical definition. In a rare outcome (eg, a disease prevalent in <10% of the population), the OR will be approximately the same as RR. However, it is defined as ‘the ratio of the relative odds of the outcome occurring in Group A compared to it occurring in Group B’ and is used when the absolute risk (risk in general population) is unknown.
Placebo	An inactive substance or preparation used as a control in an experiment or test to determine the effectiveness of a medicinal drug.
Pre-eclampsia	A pregnancy-induced condition that can occur in the second half of pregnancy. It is characterised by high blood pressure, sudden swelling along with rapid weight gain due to fluid retention, and protein in the urine.
Preterm birth	The birth of a baby of less than 37 weeks’ gestation.
Preterm labour	Labour before 37 weeks’ gestation.

p-value	Used in hypothesis testing where initially it is assumed that there is no difference between two treatments. The p-value is the probability that the difference observed in a study between the two treatments might have occurred by chance. Small p-values indicate evidence against an assumption of no difference. Large p-values indicate insufficient evidence against the assumption of no difference between treatments, not that there is no difference between treatments. Individual p-values will depend on study size; large studies can detect small differences, for example.
Postnatal	Occurring after birth; concerned with the care and treatment of the baby and pregnant women after birth.
Postpartum	The period of time after birth.
Randomised controlled trial	A comparative study in which participants are randomly allocated to intervention and control groups and followed up to examine differences in outcomes between the groups.
Reduction in risk	The extent to which a treatment reduces a risk of an outcome, in comparison with patients not receiving the treatment of interest.
Referral Guidelines	<i>Guidelines for Consultation with Obstetric and Related Medical Services</i> ¹⁰²
Regimens	A pattern of treatment such as dose or frequency of a drug.
Relative risk / risk ratio (RR)	The ratio of risks in two treatment groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is less than one indicates that the intervention was effective in reducing the risk of that outcome.
Respiratory distress syndrome	Respiratory distress usually in preterm babies, caused by developmental insufficiency of surfactant production and structural immaturity of the lungs.
Risk	The probability of an outcome that is given by the number with the outcome divided by the number with and without the outcome.

Risk of bias	Bias in the reported outcomes of a study may be caused by an inadequacy in the way the study is designed or conducted. For example, if any of the following aspects of the trial were not conducted properly then the trial may have an increased risk of bias: the random allocation of the treatments, allocation concealment, blinding of researchers during intervention and measurement of outcomes, missing outcome data, selective outcome reporting.
Sample size	The number of units (people, animals, patients, specified circumstances, etc) in a population to be studied. The sample size should be big enough to have a high likelihood of detecting a true difference between two groups.
Singleton	A single baby.
Small for gestational age (SGA)	An infant with birthweight less than the 10th birthweight centile or a fetus with an estimated fetal weight on a customised growth chart less than the 10th customised centile for gestation.
Spot urine	The sampling of a single, untimed urine specimen, voided spontaneously by the patient.
Stillbirth	Death in a fetus \geq 400 g or at least 20 weeks' gestational age.
Systematic review	A review of a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyse and summarise the results of the included studies.
Woman-centred care	Care that gives respect and dignity by supporting the woman to be central and active in her own care through: <ul style="list-style-type: none"> • holistic care taking account of the woman's physical, psychosocial, cultural, emotional and spiritual needs • focusing on the woman's expectations, aspirations and needs, rather than the institutional or professional needs • recognising the woman's right to self-determination through choice, control and continuity of care from one or more known caregivers • recognising the needs of the baby, the woman's family and significant others.

List of abbreviations

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
AFV	Amniotic fluid volume
ALT	Alanine transaminase
AOR	Adjusted odds ratio
ART	Artificial reproductive technology
AST	Aspartate transaminase
AUC ROC	Area under the receiver operating characteristics curve
BMI	Body mass index
BMJ	British Medical Journal
BP	Blood pressure
BPP	Biophysical profile
CI	Confidence interval
CKD	Chronic kidney disease
CSE	Combined spinal and epidural anaesthesia
CTG	Cardiotocograph
CVA	Cerebrovascular accident – also called a stroke
CVD	Cardiovascular disease
dBp	Diastolic blood pressure
ECG	Electrocardiogram
FBC	Full blood count
FGR	Fetal growth restriction
GA	General anaesthesia
GDT	Guideline Development Team
GP	General practitioner (family doctor)
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDP	Hypertensive disorders in pregnancy
HELLP	H aemolysis, E levated L iver enzymes and L ow P latelet count
IM	Intramuscular
IQR	Interquartile range
ISSHP	International Society for the Study of Hypertension in Pregnancy
IU	International Units
IUGR	Intrauterine growth restriction
IV	Intravenous

LDH	Lactate dehydrogenase
LFT	Liver function test
LMC	Lead maternity carer. May be a community midwife, obstetric GP or private obstetrician
NICE	National Institute for Health and Care Excellence
NNT	Numbers needed to treat
NNTH	Numbers needed to harm
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PCR	Protein:creatinine ratio
PGE2	Prostaglandin E2
PI	Pulsatility index
PIERS model	Pre-eclampsia Integrated Estimate of RiSk model
PIGF	Placental growth factor
PPROM	Preterm premature rupture of membranes
PPSMC	Pre-eclampsia Prenatal Symptom-Monitoring Scale
RCT	Randomised controlled trial
RD	Risk difference
RR	Relative risk or risk ratio
sBP	Systolic blood pressure
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
SpO2	Saturation of peripheral oxygen
TVUS	Transvaginal ultrasound
USS	Ultrasound scan
UtADV	Uterine artery Doppler velocimetry
VTE	Venous thromboembolism
WHO	World Health Organization

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Appendix A: Guideline development process

Stages in the guideline development

Developing the guideline involved the following stages, based on the GRADE approach:

- scoping the guideline (determining what the guideline would and would not cover)
- preparing the work plan (agreeing on timelines, milestones, Guideline Development Team constitution)
- forming and running the guideline development team (including terms of reference and communication plans, declaration of interests)
- developing clinical questions
- identifying evidence
- reviewing and grading evidence
- making group decisions and reaching consensus
- creating guideline recommendations
- writing the guideline
- consulting with stakeholders on the draft guideline
- finalising the guideline
- developing the implementation plan
- gaining stakeholder endorsement
- gaining ministerial approval
- publishing the guideline.

This appendix provides further detail about this process.

Purpose

The purpose of this guideline is to present recommendations based on an assessment of the research evidence with the aim of promoting the best possible clinical practices in providing care for pregnant women at risk of and/or presenting with hypertensive disorders in pregnancy and its complications. Specifically, its purpose is to improve:

- the maternal and fetal outcomes in women at risk of and/or presenting with hypertensive disorders in pregnancy and its complications
- the experience of being a patient for women at risk of and/or presenting with hypertensive disorders in pregnancy and its complications
- consistency of care provided to pregnant women at risk of and/or presenting with hypertensive disorders in pregnancy and its complications.

Scope

Target population

The target population was women at risk of and/or presenting with hypertensive disorders in pregnancy and their babies, family and whānau. This includes during pre-conception, antenatal, intrapartum and postpartum.

Settings

Community (urban-rural) settings, primary care, specialist care, emergency and critical care settings.

Developing clinical questions and identifying evidence

The Guideline Development Team (GDT) created clinical questions (Appendix D) based on the scope. The research team developed search strategies, with the search covering the period up to December 2016 and being restricted to literature in the English language.

The databases that the team searched were:

- Medline
- Embase
- CINAHL
- CENTRAL
- Cochrane Database of Systematic Reviews
- HTA database
- National Guideline Clearing House
- Guidelines International Network Database
- Te Puna
- Clinical Trials Register
- specialised register of the Pregnancy and Childbirth Cochrane Group.

The team identified New Zealand-specific via government and professional body websites, personal contacts and grey literature searching.

Search strategy

The research team used the following NICE Guideline Medical Subject Headings (MeSH) and search strategy as a basis for this search.

#	MeSH heading
1	HYPERTENSION, PREGNANCY-INDUCED/
2	PREGNANCY/ and HYPERTENSION/
3	PRE-ECLAMPSIA/
4	HELLP SYNDROME/
5	RISK/ and HYPERTENSION/ and PREGNANCY/
6	LIFE STYLE/

MeSH heading

7 DIET/

8 DIET, SODIUM-RESTRICTED/

9 exp FISH OILS/

10 VITAMINS/

11 DIETARY SUPPLEMENTS/

12 ALCOHOL DRINKING/

13 SMOKING/

14 ASPIRIN/

15 CALCIUM/

16 CALCIUM, DIETARY/

17 exp HEPARIN, LOW-MOLECULAR-WEIGHT/

18 EXERCISE/

19 EXERCISE THERAPY/

20 BED REST/

21 URINALYSIS/

22 BLOOD PRESSURE MONITORING, AMBULATORY/

23 WATER-ELECTROLYTE BALANCE/

24 VASODILATOR AGENTS/

25 ANTIHYPERTENSIVE AGENTS/

26 FETAL MONITORING/

27 METHYLDOPA/

28 LABETALOL/

29 NIFEDIPINE/

30 CALCIUM CHANNEL BLOCKERS/

31 ADRENERGIC BETA-ANTAGONISTS/

32 THIAZIDES/

33 BENZOTHIADIAZINES/

34 DIPYRIDAMOLE/

35 PREGNANCY/and HYPERTENSION/

36 PREGNANCY COMPLICATIONS, CARDIOVASCULAR/

37 exp BLOOD PRESSURE DETERMINATION/

38 exp ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/

39 exp ANGIOTENSIN II TYPE 1 RECEPTOR BLOCKERS/

40 AIIRAS.tw.

MeSH heading

- 41 exp CONGENITAL ABNORMALITIES/
- 42 FETAL GROWTH RETARDATION/
- 43 IUGR.tw.
- 44 INFANT, SMALL FOR GESTATIONAL AGE/
- 45 HEMATOLOGIC TESTS/
- 46 HEMOGLOBINS/
- 47 HEMATOCRIT/
- 48 PLATELET COUNT/
- 49 KIDNEY FUNCTION TESTS/
- 50 UREA/
- 51 CREATININE/
- 52 URIC ACID/
- 53 LIVER FUNCTION TESTS/
- 54 TRANSAMINASES/
- 55 BLOOD COAGULATION/
- 56 URINE/an [Analysis]
- 57 exp PROTEINURIA/
- 58 BLOOD COAGULATION TESTS/
- 59 BETAMETHASONE/
- 60 DEXAMETHASONE/
- 61 HYDROCORTISONE/
- 62 PREDNISONE/
- 63 exp DIAZEPAM/
- 64 PHENYTOIN/
- 65 MAGNESIUM SULFATE/
- 66 exp PHENOBARBITAL/
- 67 PARTURITION/
- 68 LABOR, OBSTETRIC/
- 69 LABOR STAGE, FIRST/
- 70 LABOR STAGE, SECOND/
- 71 LABOR STAGE, THIRD/
- 72 DELIVERY, OBSTETRIC/
- 73 exp LACTATION/
- 74 BREASTFEEDING/

#	MeSH heading
75	AMNIOTIC FLUID/
76	HEART RATE, FETAL/
77	FETAL HEART/us [Ultrasonography]
78	CARDIOTOCOGRAPHY/
79	FETAL HYPOXIA/
80	FETAL MOVEMENT/
81	ULTRASONOGRAPHY, PRENATAL/
82	ULTRASONOGRAPHY, DOPPLER/
83	UMBILICAL ARTERIES/us [Ultrasonography]
84	CEREBRAL ARTERIES/us [Ultrasonography]
85	MIDDLE CEREBRAL ARTERY/us [Ultrasonography]
86	VEINS/us [Ultrasonography]
87	HEALTH EDUCATION/or PATIENT EDUCATION AS TOPIC/

Type of studies

Where possible, the GDT used the highest possible level of evidence to inform its clinical practice recommendations. This meant, where possible, restricting evidence to clinical guidelines, systematic reviews, randomised controlled trials (for intervention questions), diagnostic studies and economic modelling studies. The GDT acknowledges that the studies in some areas, such as women's experience, do not meet these criteria and here it accepted a lower level of evidence, such as from quasi-random and observational studies.

Where studies were identified within existing systematic reviews or guidelines, the GDT did not critically appraise them, nor create an evidence table for them. Previous reviews were also excluded.

In addition, the reviews excluded the following types of publication: editorials and commentaries, publications in abstract form (including conference proceedings), personal communications and news items.

Assessment of quality of included studies

The information from systemic reviews was extracted and entered directly in GRADEpro where all parameters were available for appraisal using GRADE criteria. The quality of evidence of the systematic reviews was based on the author's assessment (using GRADE). The evidence tables present the data on the outcomes identified by the GDT and reported for the intervention in the systematic reviews, using the GRADE 'Summary of Findings' table format, for review by the GDT.

The GDT used the AGREE II tool to assess guidelines such as those of the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ), American College of Obstetricians and Gynecologists (ACOG), Society of Obstetricians and Gynaecologists of Canada (SOGC), NICE, Queensland, Australia and WHO as well as those followed in different health care settings in New Zealand.

In cases where all parameters for GRADE criteria were not available for an RCT, data was first entered and appraised using Review Manager 5.3 (Cochrane Collaboration) and exported to GRADEpro for appraisal of evidence using GRADE criteria.

Where data was not adequate for complete GRADE criteria, this guideline does not present it in evidence profile tables, but rather discusses it in the description of the evidence in the evidence statement and includes it in the 'other evidence tables'. Two reviewers assessed the quality of evidence for these studies and agreed on a grade for it. If the two reviewers could not agree on the grade, they sought the opinion of a third reviewer.

Guideline post-development

Implementation

The costs and resources involved in implementing this guideline are out of the scope of this contract (the development of guideline for the diagnosis and treatment of pre-eclampsia and hypertension in pregnancy). However, the GDT has developed an implementation plan identifying practical tools and suggestions along with potential facilitators and barriers to successful implementation and has provided it to the Ministry of Health (NZ) for consideration. Recent implementation literature has guided its development of this plan.^{365,366,367,368}

Evaluation of the guideline

The guideline has been evaluated using the AGREE II tool (December 2016). The AGREE II tool (www.agreetrust.org) evaluates the quality of clinical practice guidelines and either recommends the guideline, recommends it with provisos or does not recommend the guideline. The adapted GRADE (www.gradeworkinggroup.org) method details the volume of evidence, the methodological risk of bias, evidence of heterogeneity, directness of evidence, precision of the evidence and publication bias. Cochrane (www.cochrane.org) methodology assesses evidence based on method of randomisation, allocation concealment, blinding of participants, researchers and outcome assessors, selection and reporting bias.

We also recommend to the funders of this guideline that this guideline continues to be evaluated for its uptake, use and impact on patient outcomes (eg, using maternity clinical indicators such as the rate of eclampsia diagnosis during birth admission rates). We recommend the first evaluation occurs 12 months after the guideline's release and then regularly after that.

Review of guideline

Because a number of large studies on various aspects of pre-eclampsia diagnosis and treatment are under way, we recommend reviewing and updating this guideline within two to three years and fully revising it within five years of release.

Appendix B:

Guideline development team

Member	Organisation
Claire McLintock	Royal Australasian College of Physicians
Sheridan Massey (Chair) Jackie Reetz	New Zealand College of Midwives
Aidan O'Donnell	Australian and New Zealand College of Anaesthetists
Audrey Long	Royal Australian and New Zealand College of Obstetrics and Gynaecology
Jesse Solomon	Women's Health Action
Margaret Shanks	Royal New Zealand College of General Practitioners
Chris Mallon	Ex officio member
Alesha Smith Pauline Dawson Sheena Moosa	Inquisit Ltd (Research and clinical team)

Acknowledgement

Lesley McCowan for clinical input and review of the guidelines.

Appendix C:

Conflict of interest disclosures

Members of the Guideline Development Team were reimbursed for their time and expenses for reviewing documents and attending meetings during the development of this guideline. Members also disclosed the following additional conflicts of interest.

Type of conflict	Details
Employment	Contractor to New Zealand College of Midwives as a midwifery standards reviewer
Consultancy fees/honorarium	Consumer representation on Waitemata District Health Board
Support for travel and accommodation	Annual consumer forum – Waitemata District Health Board New Zealand College of Midwives conference 2014–World Health Assembly (WHA)

Appendix D:

Clinical questions

1. What are the clinical conditions that constitute hypertensive disorders in pregnancy (HDP)? How should HDP be diagnosed and classified? How should risk factors be classified? How should blood pressure and proteinuria be measured and classified?
2. What interventions are effective in predicting and/or preventing HDP and their complications for the mother and the fetus? How effective are lifestyle changes (rest, exercise, salt restriction), supplements (vitamin C, E and calcium) or medication (aspirin) in preventing HDP?
3. What interventions should be offered for pregnant women presenting with HDP to improve outcomes for the mother and the fetus? What interventions (lifestyle changes, supplements, antihypertensives, antiplatelet agents, anticonvulsants, corticosteroids) and in what settings?
4. What parameters (maternal and fetal) should be monitored in women presenting with HDPs? How frequently should these clinical and/or biochemical assessments of mother and fetus be carried out for different conditions of HDP and in what settings? What are the indications for referral and/or transfer of clinical responsibility (same as New Zealand Referral Guidelines)?
5. What are the indications for timing and mode of birth in women presenting with HDP? When should a strategy of expectant management be adopted? What parameters should be monitored and how frequently? What medications are effective (corticosteroids, magnesium sulphate)?
6. What is the appropriate care in the intrapartum period for women presenting with HDP? What parameters should be monitored and how frequently? What medications are effective (antihypertensives, antiplatelet agents, anticonvulsants, corticosteroids)?
7. What postpartum monitoring and advice should be given to women with HDP? What parameters should be monitored and how frequently? What medications are effective (antihypertensives)?
8. What advice should be given to improve women's experience? At first contact, antenatal visits, postnatally? What advice should be given considering the woman's rights to be fully informed and make informed choice/ decline medical advice?

Appendix E:

Prioritisation of maternal and fetal outcomes

Listed below are important outcomes for women from the management of hypertensive disorders in pregnancy. Each member of the advisory group ranked these outcomes by considering its importance for the woman. The average score for each outcome was calculated and those outcomes scoring above 6 were used in developing the evidence profiles. In applying the grade methodology, the quality of evidence was linked to the importance of the outcomes, which formed the basis of recommendations.

Outcomes	Rank
Gestational hypertension	7
Pre-eclampsia	8
Maternal death	9
Eclampsia	9
Recurrent seizures	9
Severe maternal morbidity (cerebrovascular incident, cerebral haemorrhage, myocardial infarction, kidney failure, placental abruption and pulmonary oedema)	9
Admission to intensive care unit	9
HELLP	9
Postpartum hypertension	7
Adverse effects of interventions	8
Patient experience	6
Perinatal deaths	9
Admission to neonatal intensive care unit/ nursery	9
Small for gestational age fetus	7
Neonatal complications (eg, hypoglycaemia, hypothermia, hypotension, feeding difficulties, jaundice and neonatal bradycardia)	7
Preterm birth <34weeks	8

Appendix F: Summary of GRADE approach

The GRADE Approach

More about strength of recommendation and quality of evidence

Strength of recommendation The extent to which the CPG Work Group is confident that benefits of the recommended intervention outweigh its harms (or vice versa)

STRONG → Benefits clearly outweigh risks and burdens (or vice versa)
Can be interpreted as:

- most clients should be offered the intervention, assuming that they have been informed about and understand its benefits, harms and burdens
- most clients would choose the recommended course of action and only a small proportion would not.

WEAK → Benefits, risks and burdens are closely balanced
Can be interpreted as:

- the majority of clients would choose the suggested course of action, but an appreciable proportion would not.
- values and preferences vary widely.

Based on (1,4–6)

QUALITY OF EVIDENCE How certain we ought to be about an estimate of effect or association

HIGH	Further research is very unlikely to change confidence in the estimate of effect. → Benefits clearly outweigh risks and burdens (or vice versa)	Decision-making around quality of evidence is influenced by the following factors:
MODERATE	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate. → This evidence provides a good basis for decision-making	<ul style="list-style-type: none"> • study design • study quality • consistency across studies
LOW	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate. → This evidence provides some basis for decision-making	<ul style="list-style-type: none"> • directness of population, intervention, or outcome • precision in estimates of effect
VERY LOW	Any estimate of effect is very uncertain. → This evidence does not provide much of a basis for decision-making	<ul style="list-style-type: none"> • effect size • presence of a dose-response effect.

Association of Ontario Midwives www.aom.on.ca/files/Health_Care_Professionals/Clinical_Practice_Guidelines/GRADE_tool_v2.pdf