Te Whatu Ora
Health New Zealand

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

Te Tautohu, Te Tumahu i te Toto Pōrutu me te Pēhanga Toto Kaha i te Hapūtanga ki Aotearoa

Evidence statements

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1 Executive summary

This document provides the evidence statements used to develop the recommendations in the guideline, *Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand*. These evidence statements inform the guideline's recommendations and provide key information, such as:

- a summary of available data on important outcomes relating to hypertensive disorders in pregnancy (HDP)
- 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.

2 Research recommendations

The evidence statements identified the following research recommendations.

1. The National Institute for Health and Care Excellence (NICE) in the United Kingdom 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 of these evidence statements, the evidence on the balance of costs and benefits of using these tests in an Aotearoa New Zealand setting were still being 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 pregnant women/people with HDP. This includes determining which frequency and settings for monitoring provide the best balance between costs and benefits, as well as providers' and pregnant women/people's preferences for different approaches.
4. Very few research findings are available on the educational and support needs of pregnant women/people at high risk of pre-eclampsia or of those experiencing HDP.
5. The evidence relating to specific population groups' experience of hypertension and pre-eclampsia in Aotearoa New Zealand is sparse. Further Aotearoa New Zealand-

based evidence of the impact of HDP is needed. This should include evidence of the prevalence of hypertensive disorders in specific populations and inequities in care and outcomes for specific populations (for example, delays in diagnosis by ethnicity or rurality).

3 Classifications and clinical definitions

The purpose of classifying HDP and defining related terms is to create clear categories that reflect the risks and potential outcomes for the pregnant woman/person[1] and their baby and so can guide clinical management. Clear classifications also enable accurate record keeping and help with research aimed at improving outcomes for pregnant women/people and their babies.

While existing clinical practice guidelines on the topic differ in the range of conditions, they include in classifying and defining HDP, those differences are few (Lowe et al 2015; Magee et al 2014; NICE 2010; Task Force on Hypertension in Pregnancy 2013; Regitz-Zagrosek et al 2011). Where guidelines differ, the evidence statements are based on expert opinion, such as the statements from expert groups from the International Society for the Study of Hypertension in Pregnancy (ISSHP). HDP is classified 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.

These conditions are discussed in more detail below.

[1] To be consistent with other maternity clinical guidelines, gender additive language (pregnant women/ person) is used the evidence statement. The term woman/women has been used alone in relation when referring to specific research as this retains consistency with the published findings.

Several guidelines do not include postpartum hypertension in classifying HDP. However, studies have recognised that, in addition to the peak rise in blood pressure (BP) between the third and fifth day postpartum, new onset hypertension can develop from two weeks to six months after birth (NICE 2010; ACOG 2013). For this reason, these evidence statements draw attention to the conditions classified as HDP in the postpartum period (Magee and von Dadelszen 2013).

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' 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 pregnant woman/person who had normal BP before 20 weeks' gestation) and:

- sBP is ≥140 mmHg **or** dBP is ≥90 mmHg
- the pregnant woman/person has none of the abnormalities that define pre-eclampsia
- their BP returns to normal within three months after giving birth.

White coat hypertension

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

Degrees of hypertension

- Mild/moderate hypertension is when dBP is 90–109 mmHg **or** sBP is 140–159 mmHg.
- Severe hypertension is when dBP is ≥110 mmHg **or** sBP is ≥160 mmHg.

In existing clinical practice guidelines and research definitions of severe hypertension, the reference to cut-off levels in sBP differs, with some using a reference of 160 mmHg and others using 170 mmHg sBP (Lowe et al 2015; Magee et al 2014; NICE 2010; Task Force on Hypertension in Pregnancy 2013; Gillon et al 2014). These evidence statements use sBP of ≥160 mmHg to be consistent with the ISSHP definition (Tranquilli et al 2013).

On the practice of taking two consecutive measurements at least four hours apart, expert opinion is that such a strategy may lead to delays in appropriate care for severe hypertension. Therefore, in severehypertension, clinical judgement about measuring more frequently should be applied (for example, every 15 minutes and then every 30 minutes in the initial phase of assessment) (Magee et al 2014; Gillon et al 2014).

Pre-eclampsia

The new onset of hypertension occurs after 20 weeks' gestation (in a pregnant woman/person who had normal BP before 20 weeks' gestation) or is 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 ≥2+ on dipstick testing confirmed by a protein:creatinine ratio test
2. other maternal organ dysfunction:
    a) renal insufficiency (creatinine >90 µmol/L, urine output of <80mL/4hr)
    b) liver involvement (elevated transaminases (ALT and AST) at least twice the upper limit of normal ± right upper quadrant or epigastric abdominal pain)

        Note: Normal ranges are: ALT 0–30 u/L and AST 10–50 u/L

    c) neurological complications (for example, eclampsia, altered mental status, blindness, stroke or, more commonly, hyperreflexia when accompanied by clonus, severe headaches and persistent visual scotomata)
    d) haematological complications (thrombocytopenia – platelet count below 100 x 10^9/L, haemolysis)
3. uteroplacental dysfunction (fetal growth restriction, FGR).

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 × 10^9/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 ± 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

This condition relates to pregnant women/people with pre-eclampsia who have worsening pre-eclampsia blood results and severe hypertension not easily controlled with antihypertensives. The condition is also known asfulminating 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 severefeatures develop, it is prudent to recommend managing the pregnant woman/person, at least initially, as an inpatient in a centre with a maternal and neonatal high-dependency or intensive care unit (Steegers et al 2010).

Notes

- **Severity of proteinuria**: The issue of the severity of proteinuria is critical as there is no clear evidence or consensus around what amount of proteinuria is ‘severe’ (Gillon et al 2014; Tranquilli et al 2013). Although the majority of current guidelines on pre-eclampsia rely on values between 3 and 5 g/L, evidence shows no association between the level of proteinuria and progression of the disease (Homer et al 2008; Thornton et al 2010). 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 (Lowe et al 2015; Magee et al 2014; NICE 2010; Task Force on Hypertension in Pregnancy 2013; Regitz-Zagrosek et al 2011).
- **FGR**: Historically, worsening FGR was seen to be a severe feature of pre-eclampsia. However, because the management of FGR is similar in non-pre-eclamptic women, the current opinion is not to include FGR as a severe feature of pre-eclampsia (Task Force on Hypertension in Pregnancy 2013).
- **Proteinuria**: Although proteinuria is the most common feature of pre-eclampsia that distinguishes it from gestational hypertension (North et al 1999), the current evidence suggests that proteinuria is not an absolute requirement for establishing the diagnosis of pre-eclampsia (Lowe et al 2015; Magee et al 2014; ACOG 2013; Tranquilli et al 2013). 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 FGR in the absence of proteinuria (Homer et al 2008; Thornton et al 2010). It is possible to diagnose pre-eclampsia after establishing a pregnant woman/person has hypertension and new onset proteinuria **or** when they have 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 (Tranquilli et al 2013; Côté et al 2008). 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 (Brown et al 1995; Phelan et al 2004; Waugh et al 2001). 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 (Lowe et al 2015; Magee et al 2014).
- **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 (Lindheimer and Kanter 2010). 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 (Tranquilli et al 2014; Lowe et al 2015; Magee et al 2014; NICE 2010).
- **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 (Tranquilli et al 2014; Lowe et al 2015).
- **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 (Tranquilli et al 2014; Lowe et al 2015; Magee et al 2014; Gillon et al 2014).
- **Neurological involvement**: The criteria of neurological involvement are based on clinical symptoms and examination (Lowe et al 2015; Magee et al 2014; NICE 2010; Task Force on Hypertension in Pregnancy 2013). 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 × 10^9/L (Lowe et al 2015; Gernsheimer et al 2013). However, other

existing clinical practice guidelines use the cut-off level for an abnormal platelet count in pre-eclampsia as <100 × 10^9/L (Lowe et al 2015; Magee et al 2014; NICE 2010; Task Force on Hypertension in Pregnancy 2013). The ISSHP's cut-off level in the diagnostic criteria of pre-eclampsia (<150 × 10^9/L) differs from the level for HELLP (<100 × 10^9/L) (Tranquilli et al 2014; Tranquilli et al 2013). It is likely that differences arise from different classification systems used for HELLP (Haram et al 2009; Martin et al 2013). Indications of haemolysis include red cell fragments on blood film, raised bilirubin, raised lactate dehydrogenase >600 IU/L and decreased haptoglobin (Magee et al 2014; Task Force on Hypertension in Pregnancy 2013).

- **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 (Hawkins et al 2012; Bellomo et al 2011; von Dadelszen et al 2011). 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 (Koopmans et al 2009b). Māori have a statistically significantly higher prevalence of hyperuricaemia (serum units >0.40 mmol/L) compared with non-Māori (17.0% compared with 7.5%, p = 0.0003) (Stamp et al 2013).
- **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 (Chung et al 2009).

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 pregnant women/people.

Up to 44% of eclamptic seizures occur after birth (Magee and von Dadelszen 2013). 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 (Magee et al 2014; Task Force on Hypertension in Pregnancy 2013).

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 pregnant woman/person with pre-eclampsia, the presence of any of the following is an indicator of HELLP:

- maternal platelet count of less than 100 ū× 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 HDP.

4 Risk factors

Risk factors for pre-eclampsia – recommendations

As early as possible in the pregnancy or when the pregnant woman/person books for antenatal services, identify risks for HDP as part of the full health assessment (see table 1, Risk ratio for developing pre-eclampsia in a pregnant woman/person with pre-existing risk factors below).

Strong recommendation; low-quality evidence

Refer pregnant women/people with pre-existing hypertension for consultation with an obstetrician, ideally before 16 weeks' gestation.

Strong recommendation; low-quality evidence

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 (Anderson et al 2012; Duckitt and Harrington 2005; Thilagnathan 2016). 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 (Kenny et al 2014). It is important to identify risk factors early so that the pregnant woman/person can then receive appropriate monitoring and treatment.

Previous history of HDP 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; 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) (Chames et al 2003).

One study (536 women) demonstrated that the prevalence of chronic hypertension was higher among women who developed pre-eclampsia than among those who did not (12.1% compared with 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 (SGA) age infants (OR 5.6; 95% CI 1.8–16.0) and birth before 32 weeks' gestation (OR 15.0; 95% CI 5.7–38.0) than women with chronic hypertension without superimposed pre-eclampsia (McCowan et al 1996).

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; 3.60; 95% CI 1.49–8.67 from case-control studies) (Duckitt and Harrington 2005). In this review, 'family history' has focused on the mother of the pregnant woman (Duckitt and Harrington 2005). However, other studies and ongoing research indicate that a family history should include the woman's sister: RR of family history (mother or sister) positive compared with family history negative for total pre-eclampsia was 3.4 (95% CI 1.5–7.6; p = 0.018); and RR for severe pre-eclampsia was 4.3 (95% CI 1.6–11.5; p = 0.017) (Cincotta and Brennecke 1998). 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 and those with gestational hypertension were 1.6 times (95% CI 1.3–2.0) more likely to have a sister with gestational hypertension (Carr et al 2009).

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 OR 2.1 (95% CI 1.0–4.3; p = 0.04), (Esplin et al 2001)An aetiology of these findings is available in a review by Dekker et al (2011). Ongoing genetic research, including Australasian studies, also support this evidence (Moses et al 2015).

Table 1: Increased risk of developing pre-eclampsia in pregnant women/people with pre-existing risk factors

Pre-existing risk factor	Relative risk/ odds ratio	95% CI
Major risk factors		
Antiphospholipid antibodies / SLE	9.7[b]	4.3–21.7
Previous history of pre-eclampsia	7.2[b]	5.9–8.8
ART (oocyte donation) (Masoudian et al 2016)	4.3[a]	3.1–6.1

Renal disease (Fischer et al 2004)	4.1[a]	2.2–7.7
Chronic hypertension	3.6[a]	2.0–6.6
Previous history of HELLP (Chames et al 2003)	3.7[a]	0.9–16.1
Pre-existing diabetes	3.6[b]	2.5–5.0
Family history of pre-eclampsia in mother or sister	3.3	1.5–7.4
Other risk factors		
Nulliparity	2.9[b]	1.3–6.6
Multiple pregnancy	2.9[b]	2.0–4.2
Family history of pre-eclampsia	2.9[a]	1.7–4.9
Father of baby (born of a pregnancy complicated by pre-eclampsia) (Esplin et al 2001)	2.1	1.0–4.3
Genetic ancestry – African (Poon et al 2010)	3.0[a]	2.0–4.4
– Indian	2.7[a]	1.3–5.5
– Māori (Anderson et al 2012)	1.5[a]	1.2–2.0
– Pacific	1.2[a]	1.0–1.6
Change in partner (Trupin et al 1996)	2.5[b]	1.8–3.5
Elevated BMI ≥35 years (early/pre-pregnancy)	2.5[a]	1.8–3.2
Maternal age ≥40 years (multiparous)	2.0[b]	1.3–2.9
Maternal age ≥40 years (nulliparous)	1.7[b]	1.23–2.29
Pregnancy interval >10 years	1.8[b]	1.72–1.94
ART (sperm donation) (González-Comadran et al 2014)	1.6[a]	1.36–1.95
Diastolic BP ≥80 mmHg at booking	1.4[b]	1.01–1.87
Any ART (Wang et al 2016)	1.2[a]	1.10–1.24

a. Adjusted odds ratio. b. Relative risk. Data from Duckitt and Harrington 200522 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; SLE = systemic lupus erythematosus.

Pre-existing medical conditions

The evidence shows that a pregnant woman is almost four times more likely to develop pre-eclampsia if they 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 who do not (unadjusted OR 4.07; 95% CI 2.17–7.66) (Fischer et al 2004). 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 those without CKD (Nevis et al 2011).

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 them 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 antibodies (Duckitt and Harrington 2005).

4.1 Factors related to the woman/person and the pregnancy

Age

Women aged 40 years or older 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-eclampsia (Duckitt and Harrington 2005).

Ethnicity

A study of 26,254 women in Aotearoa 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 (adjusted OR 0.56; 95% CI 0.41–0.76) and nearly 50% higher among Māori (adjusted OR 1.51; 95% CI 1.16–1.96); the risk is also higher among Pacific women (OR 1.44; 95% CI 1.20–1.74) and Indian women (OR 1.35; 95% CI 1.05–1.73) (Anderson et al 2012). 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) (Poon et al 2010).

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) (Duckitt and Harrington 2005). 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 women with excessive weight gain, but especially those with high BMI (in relation to Institute of Medicine guidelines, see Rasmussen and Yaktine 2009), 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 (Truong et al 2015). A study of Chinese women found that the impacts of high BMI on pre-eclampsia (as well as gestational diabetes and preterm birth) might be stronger for Chinese women than for Caucasian women (Leung et al 2008).

This evidence points to the importance of appropriate gestational weight gain in pregnancy in reducing the risk of the pregnant woman/person developing HDP and other pregnancy complications.

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 three or more and that nulliparity almost triples the risk for pre-eclampsia (unadjusted RR 2.91; 95% CI 1.28–6.61) (Duckitt and Harrington 2005). A longer interval (more than 10 years between pregnancies) has also been associated with a significantly higher risk of pre-eclampsia in a subsequent pregnancy when pre-eclampsia had not been present in the first pregnancy. However, when the interpregnancy interval was 10 years or less, the risk of pre-eclampsia was about the same as that in nulliparous women (Duckitt and Harrington 2005; Skjaerven et al 2002). 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) (Skjaerven et al 2002).

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) (Trupin et al 1996).

Twin pregnancies

In twin pregnancies, the risk of pre-eclampsia nearly triples (unadjusted RR 2.93; 95% CI 2.04–4.21) (Duckitt and Harrington 2005).

Fertility treatment

Evidence from a retrospective cohort study indicated that the risk of gestational hypertension/pre-eclampsia was higher among women who used assisted reproductive technology (ART) compared with those who had nott (adjusted OR 1.17; 95% CI 1.10–1.24) (Wang et al 2016). A recent systematic review compared pregnancy complications of donor oocyte pregnancy with autologous oocyte in vitro fertilisation. It found that the risk of developing a hypertensive disorder of pregnancy was significantly higher for donor oocyte pregnancy (OR 3.92; 95% CI 3.21–4.78) (Jeve et al 2016). Supporting this evidence, another systematic review found that the risk of pre-eclampsia is higher in oocyte-donation pregnancies compared with other methods of ART (OR 2.54; 95% CI 1.98–3.24, $p < 0.0001$) or natural conception (OR 4.34; 95% CI 3.10–6.06, $p < 0.0001$) (Masoudian et al 2016). 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) (González-Comadran et al 2014).

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 a separate screening test, which produces additive detection and false positive rates (Poon et al 2010). 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 (Poon et al 2010; North et al 2011).

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 medicines. On the other hand, higher maternal age, BMI and family history or history of pre-eclampsia were predictors of late pre-eclampsia (34 weeks' gestation and after) and gestational hypertension (Poon et al 2010). 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 rate (Poon et al 2010).

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 (North et al 2011). Most women in this study were from Aotearoa New Zealand. The algorithm included risk factors (BP, 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. Adding information from ultrasonography did not significantly improve the performance of the algorithm, with an AUC ROC of 0.77 (North et al 2011). The sensitivity and specificity of the risk scores at 14–16 weeks' gestation 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 positive likelihood ratio (LR)+5.5 (4.2–7.2), LR–0.76 (0.70–0.84) (North et al 2011). With a cut-off value of 10% false positive, 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, 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) (North et al 2011). 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 indicates that using algorithms to predict pre-eclampsia provides the first step towards a personalised risk prediction algorithm. However, it is essential to gather further high-quality evidence and get external validation of the algorithms in other populations.

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

5 Prediction – biomarkers and ultrasonographic markers

Predictive testing – recommendations

Tools that combine different biochemical markers and uterine artery Doppler for predicting pre-eclampsia are not currently recommended for routine use.

Note: the use of the sFlt-1/PlGF ratio is currently being assessed in the Aotearoa New Zealand context, and this recommendation will be reviewed once further evidence is available.

Weak recommendation; very low-quality evidence

While research in this area is promising, current evidence around the use biomarkers and uterine artery Doppler in predictive models is insufficient to recommend their use in clinical practice.

There is some evidence that maternal factors and maternal medical history can strengthen the predictive capability of biomarkers or ultrasonographic markers alone. Risk factors like type 1 diabetes and medical history of HDP may also help predicting HELLP syndrome. More research is needed for predictors of both early-onset and late-onset pre-eclampsia to draw a further conclusive recommendation.

5.1 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 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) which generates various responses, such as immune responses, and influences other functions like apoptosis and molecular recognition, (Rana et al 2012; Verlohren et al 2014; Zeisler et al 2016; Zhong et al 2015).
- hCG (human chorionic gonadotropin), a hormone the placenta produces during pregnancy
- MPV (mean platelet volume), a potential biomarker for pre-eclampsia given that pre-eclampsia is characterised by an increased platelet consumption with consecutive reduction of overall platelet count and a consecutive rise in MPV
- serum cystatin-c, a protein associated that increases during the third trimester of normal pregnancy.

The current evidence around biomarkers is of moderate to low quality. It is important to interpret the evidence with caution when considering the biomarkers' 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 (Zhong et al 2015). 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) (Zhong et al 2015).
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) (Zhong et al 2015).
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) (Zhong et al 2015).

A systematic review of individual biomarkers also observed that PlGF is a morepromising 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% 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) (Wu et al 2015).

Other biomarkers, such as **hCG**, **ADAM** and **Inhibin A** have been tested for their ability to predict pre-eclampsia. They all show poorer results than PlGF (Zhong et al 2015; Wu et al 2015).

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 (Rana et al 2012; Verlohren et al 2014; Zeisler et al 2016). Verlohren et al (2014) conducted a case-control study 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, that showed varying results for different gestational ages.

- At gestation of more than 20 weeks, the sensitivity of the test was 76% and specificity was 95%.
- 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 late gestation (≥34 weeks), the s-Flt-1:PlGF ratio at ≥110 was 58% sensitivity and 95% specificity respectively (Verlohren et al 2014).

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 study points to an approach with different cut-off levels of s-Flt-1:PlGF ratio based on the gestational phase in predicting pre-eclampsia (Verlohren et al 2014).

Another study observed that the 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) (Rana et al 2012). 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 (that is, no pre-eclampsia in the subsequent week) of 99.3% (95% CI 97.9–99.9)

(Zeisler et al 2016). 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).

One moderate quality systematic review (Agrawal et al 2019) reported that serum PlGF is a useful tool in predicting PE. It concluded that predictive values were highest for PlGF values between 80 and 120 pg/mL:

- a high predictive odds ratio (OR) of 25 (range of values = 7–88)
- sensitivity of 0.78 (95% CI 0.67-0.86)
- specificity of 0.88 (95% CI 0.75-0.95)
- LR+ 6.3 (95% CI 2.7-14.7)
- LR- 0.26 (95% CI 0.16-0.42).

Additionally, the accuracy of the PlGF was higher when the test was performed after 14 weeks' gestation (OR 10; 95%CI 7-15) and for prediction of early onset pre-eclampsia (OR 18 95% CI: 9-37).

Two studies concluded that s-Flt-1:PlGF ratio was also a useful predictor of pre-eclampsia. One prospective cohort study (Sovio et al 2017) reported the following for an s-Flt-1:PlGF ratio of >38:

- at 28 weeks' gestation: positive predictive value (PPV) of 32% for pre-eclampsia and preterm birth, with a similar power for women with low and high previous risk of disease
- at 36 weeks' gestation: PPV for severe pre-eclampsia of 20% in high-risk women and 6.4% in low-risk women.

At 36 weeks' gestation, an sFlt-1:PlGF ratio >110 had a PPV of 30% for severe pre-eclampsia, and the PPV was similar comparing low- and high-risk women. A prospective study assessed the MPV in women with pre-eclampsia compared with healthy controls as a predictor of pre-eclampsia (Mayer-Pickel et al 2021). MPV values were validated against s-Flt-1:PlGF ratio as common markers of pre-eclampsia and normal pregnancies. The authors reported that s-Flt-1:PlGF was predictive of both early- and late-onset pre-eclampsia, however, MPV was predictive of only early-onset pre-eclampsia (that is, before 34 weeks' gestation) ($p<0.05$).

One meta-analysis reported that serum cystatin-c is a promising biomarker in predicting pre-eclampsia during the third trimester (Magee and von Dadelszen 2013). Serum cystatin-c levels were higher in pre-eclamptic women compared with healthy pregnant controls:

- mean difference: 0.40 mg/L (95% CI 0.33, 0.46)
- pooled sensitivity: 0.85 (95% CI 0.79, 0.89)

- pooled specificity 0.84 (95% CI 0.77–0.90).

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 the 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.

5.2 Ultrasonographic markers – uterine artery Doppler velocimetry abnormalities

The trophoblast invasion of the spiral arteries, leading to maldevelopment of uteroplacental perfusion underlying the pathophysiology of pre-eclampsia, suggests that assessment of uterine artery flow has the potential to predict pre-eclampsia (Velauthar et al 2014; Myatt et al 2012).

A meta-analysis of 18 studies (of 55,974 women) evaluated the accuracy of first-trimester uterine artery Doppler velocimetry (UADV) (between 11- and 14-weeks' gestation) to predict poor pregnancy outcomes, including pre-eclampsia and fetal growth restriction (FGR) (Velautar et al 2014). In predicting early-onset pre-eclampsia, abnormal uterine artery flow velocity waveform 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 FGR, its sensitivity was 39.2% (95% CI 26.3–53.8) and its specificity was 93.1% (95% CI 90.6–95.0) (Velauthar et al 2014). Another cohort study (of 2,188 low-risk nulliparous women <21 weeks' gestation) demonstrated that second trimester UADV has poor sensitivity for predicting pre-eclampsia (Myatt et al 2012), yet a meta-analysis of 74 studies of pre-eclampsia (total 79,547 women) demonstrated that UADV provided a more accurate prediction of pre-eclampsia in the second trimester than in the first trimester and is dependent on the indices used (Cnossen et al 2008). This meta-analysis showed that most Doppler indices had poor predictive characteristics. One pooled estimate analysis (351 women) 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).

One prospective cohort study3 showed first-trimester uterine artery (UtA) PI measured by Doppler's ultrasound to be a predictor of preterm pre-eclampsia (Demers et al 2019). First-trimester mean UtA-PI was associated with preterm pre-eclampsia (AUC: 0.69; 95% CI: 0.57, 0.80) but not with term pre-eclampsia (AUC: 0.52; 95% CI: 0.48, 0.56). UtA-PI combined with maternal characteristics could predict 45% of preterm pre-eclampsia at a false positive rate of 10%.

Although the evidence indicates UADV 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 UADV in assessing the risk of pre-eclampsia.

5.3 Combination of biomarkers, UADV and maternal factors

A systematic review of 37 observational studies among low-risk populations assessed the predictive performance of a combination of predictive tests (Giguère et al 2010). 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 UADV 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 UADV and serum PlGF <188 pg/mL at 20–22 weeks' gestation 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%) (Ghosh et al 2012). Evidence from another cohort study assessed the predictability of UADV with different PlGF cut-off levels (<280 pg/mL and >280 pg/mL) in women at 22–26 weeks' gestation. Women with abnormal UADV 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 UADV results and those with abnormal UADV results and a PlGF ≥280 pg/mL (chi square for trend; p < 0.001) (Espinoza et al 2007).

A pooled analysis of prospective screening studies (Tan et al 2018)F and a further prospective cohort study (Mazer Zumaeta et al 2020) reported that maternal factors (maternal characteristics and medical history) in combination with UtA-PI, MAP and PlGF in the first trimester can predict a high proportion of pregnancies that develop early pre-eclampsia or preterm pre-eclampsia. Using a screen-positive rate of 10%, combined screening by maternal factors, MAP, UtA-PI and PlGF predicted:

- 90% of pre-eclampsia with birth at < 32 weeks' gestation (Tan et al 2018)
- 84% of pre-eclampsia with birth at < 34 weeks' gestation (Mazer Zumaeta et al 2020)
- 74% (Mazer Zumaeta et al 2020) and 75% (Tan et al 2018) of pre-eclampsia with birth at <37 weeks' gestation

- 44% (Mazer Zumaeta et al 2020) and 42% (Tan et al 2018) of pre-eclampsia with birth at ≥ 37 weeks' gestation.

Both studies reported that including PAPP-A did not improve screening performance (Tan et al 2018; Mazer Zumaeta et al 2020).

A further small prospective observational study (n=37 participants) (Allen and Aquilina 2018) reported that first trimester maternal characteristics and medical history were associated with pre-eclampsia or gestational hypertension, but biomarkers or ultrasonographic markers (UtA-PI, PlGF, PAPP-A) were not. These findings (Allen 7 Aquilina 2018), were contrary to other studies that reported good PPV for UtA-PI and PlGF and the difference was attributed to low prevalence of pre-eclampsia or pregnancy-induced hypertension in the study. One prospective study (Panaitescu et al 2018) found that the additive effect of maternal factors (demographic characteristics and medical history) in combination with MAP, PlGF and s-Flt-1 in the third trimester could predict up to 70% of pregnancies that will develop pre-eclampsia. The authors reported that screening performance was not improved by the addition of UtA-PI.

In the first trimester, maternal factors (maternal characteristics and medical history) in combination with biomarkers (PlGF, MAP) and ultrasonographic markers (UtA-PI) predict a high proportion of pregnancies with pre-eclampsia. In the third trimester, maternal factors combined with biomarkers (PlGF, MAP, s-Flt-1), but not ultrasonographic markers (UtA-PI), could predict up to 70% of pregnancies that will develop pre-eclampsia.

One prospective study of Asian women (Chaemsaithong et al 2020b) showed that first-trimester MAP and PlGF, but not UtA-PI, were significantly lower in Asian women than their European counterparts. This study indicated that biomarker adjustment factors or population-specific biomarkers may be warranted.

One prospective cohort study (Malmstrom and Morken 2018)9 reported that type 1 diabetes and a BMI of 30 kg/m2 were associated with HELLP syndrome in a first pregnancy but not in a second pregnancy. The authors also reported that chronic hypertension and multiple pregnancy were associated with HELLP syndrome in both a first and a second pregnancy and that a history of HELLP syndrome or preterm eclampsia were risk factors for HELLP syndrome in a second pregnancy.

5.4 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: BP, a family history of pre-eclampsia and a history of fertility treatment. The combination of UADV (20 weeks5' gestation), PlGF (15 weeks) and endoglin (20 weeks) did not significantly improve the 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) (Myers et al 2013).

5.5 Other factors: Clinical use, cost-effectiveness and the pregnant woman/person'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 UADV in addition to the current practice of a first-trimester scan would cost an additional £18–25 (Velauthar et al 2014). Although the false-positive rate is low for UADV, 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 (for example, 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 biomarker tests have 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 pregnant women/people's choices need to be considered when deciding whether to support the possible use of predictive tests.

6 Pregnant women/people's experience and engagement

Women/pregnant people's experience and engagement – recommendations

Develop and make available educational tools to help pregnant women/people understand issues relating to hypertension in pregnancy and pre-eclampsia. These tools should consider the pregnant women/people's different levels of health literacy, ethnicity, familiar language and demographic diversity.
Strong recommendation; very low-quality evidence

Work is needed to ensure equity of care for all pregnant women/people, in particular, Māori, Pacific and Asian (Indian) pregnant women/people who are over-represented in poor obstetric outcomes. Maternity services should collect and report accurate ethnicity information about maternity care and outcomes.
Strong recommendation; very low-quality evidence

Actively involve pregnant women/people and their whānau and keep both parties informed throughout the health decision-making process.
Strong recommendation; very low-quality evidence

Assess, address and document pregnant women/people's need for psychological care and support following a severe HDP.
Strong recommendation; very low-quality evidence

Offer a referral to support agencies to all pregnant women/people with pre-eclampsia, for example, social support agencies and Māori or Pacific providers, including postnatally.
Good practice recommendation

Assess and address barriers to effective communication with vulnerable groups of pregnant women/people, for example, literacy, language, geographical, socioeconomic and cultural barriers.
Good practice recommendation

Screen for postnatal depression.
Strong recommendation; very low-quality evidence

Give pregnant women/people 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; low-quality evidence

A range of activities can help build understanding of pregnant women/people's experiences by capturing direct feedback from the pregnant woman/person, 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 pregnant women/people in decisions about their own care, as well as how to run services and, increasingly, prioritise services. Because Aotearoa New Zealand studies of women/people's experience of pre-eclampsia and hypertension in pregnancy are rare, the evidence presented below mainly comes from international research. These findings may have limited relevance to Aotearoa New Zealand and may not easily translate to this context because Aotearoa New Zealand's health care and maternity system and its ethnic mix are unique.

6.1 Knowledge

The experience of pregnancy is often laced with anxiety for pregnant women/people with pre-eclampsia. Research has demonstrated that women with HDP have a generally poor understanding of the signs and symptoms of pre-eclampsia, which may explain why they do not seek timely care. An Australian study (112 members of a 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 (East et al 2010). On the other hand, a qualitative study showed that women with an increased risk of pre-eclampsia would be willing to engage in efforts to reduce that risk (Makowharemahihi 2014). However, the study also found that the women identified as at risk of pre-eclampsia fell into two 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 (Makowharemahihi 2014). 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 earlier (East et al 2010), women's experiences made them substantially more anxious about future pregnancies and partners, friends and relatives similarly expressed fear for the woman and/or their baby and had no previous understanding of pre-eclampsia. Women wanted access to information about pre-eclampsia because their pre-eclampsia experience had a substantial effect on them, their confidants and their babies, as well as on their approach to future pregnancies (East et al 2010).

A study in the United States of America (USA) 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 their pre-eclampsia knowledge, and only 14% of the women were able to provide a definition that correctly reflected the syndrome (You et al 2012).85 This study observed that women tended to get more correct answers to the questionnaire if they had higher literacy, multiparity, a history of pre-eclampsia and had received information about pre-eclampsia from a clinician or another information source (for example, the internet, television, a book or a friend) (You et al 2012).

A Brazilian study used a word-association test to explore perceptions of pre-eclampsia. The words that pregnant and postpartum women tended to associate with pre-eclampsia were ‘fear’, ‘risk’, ‘care’ and ‘lack of information’, while health professionals related pre-eclampsia more closely to aspects of care. The findings suggest a gap in the experiences of pre-eclampsia (Azevedo et al 2009).

6.2 Pre-eclampsia and mental health

A link between depression and pre-eclampsia before pregnancy

Current evidence suggests that hypertension in pregnancy is linked to maternal depression and anxiety. A 2015 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 (Thombre et al 2015). In addition, the researchers observed that chronic hypertension was the main driver behind these associations (adjusted OR = 2.7–3.5). The study also linked pre-eclampsia accompanied by preterm birth to women’s lifetime history of depression symptoms (OR 2.3; 95% CI 1.0–5.2).

Postpartum mental health

Other studies have linked post-traumatic stress disorder (PTSD) after birth with women who had pre-eclampsia or HELLP (Stramrood et al 2011; Hoedjes et al 2011; van Pampus et al 2004). A longitudinal evaluation (of 175 women) showed that at six weeks after birth, the prevalence of PTSD, but not depression, was significantly higher in these women than in a control group (14% compared to 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 (Stramrood et al 2011). Another study (of 149 women) showed that the prevalence of PTSD was 8.6% at six weeks and 5.1% at 12 weeks postpartum (Hoedjes et al 2011). 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 of experiencing PTSD (van Pampus et al 2004).

Another finding is that pregnant women/people 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 severe pre-eclampsia had a lower quality of life at six weeks postpartum than those who had mild pre-eclampsia (all $p < 0.05$), but this improved on almost all the health scales from 6–12 weeks postpartum ($p < 0.05$) (Hoedjes et al 2011). In this study, women who had mild pre-eclampsia had a poorer emotional quality of life at 12 weeks postpartum ($p < 0.05$) than those who experienced severe pre-eclampsia. The experiences of admission to the neonatal intensive care unit (NICU) and perinatal death were identified as the factors contributing to this poorer quality of life (Hoedjes et al 2011).

These studies indicate that women who have pre-eclampsia and its complications should receive appropriate postpartum psychological care and behavioural interventions (Stramrood et al 2011; Hoedjes et al 2011). Researchers have suggested that contact with other women who have had severe disease could be potentially effective as a behavioural therapy intervention (van Pampus et al 2004). However, according to one systematic review of 14 studies on midwifery interventions to reduce PTSD following birth, the evidence is insufficient to support the recommendation of any midwife-led intervention to address postpartum PTSD (Borg et al 2014). Another important consideration is how the condition and the pregnancy event in general affect the woman's family/whānau (Stramrood et al 2013).

6.3 Education

Education for maternity caregivers

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

- educational strategies with medical providers are 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 (Chaillet et al 2006).

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 HDP (Repke et al 2002). As a first step in educating pregnant women/people and providing the best care, health care providers need to be more uniform in their knowledge and approach to HDP. Research also indicates that overcoming traditionally unequal clinician-patient power relationships so that they work in partnership improves communication around high-risk pregnancies (Pozzo et al 2010).

Education for pregnant women/people

A systematic review of 13 peer-reviewed qualitative studies on antenatal education examined women's views and experiences. It demonstrated that pregnant 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 (Nolan 2009). In addition, researchers observed that 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 (Nolan 2009). This indicates that 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 (for example, headaches, blurred vision and epigastric pain). Furthermore, keeping women informed on the rationale behind the tests (for example, laboratory analysis, non-stress test) and treatments (for example, magnesium sulphate, antihypertensive) specific to the individual may help alleviate stress and anxiety during an emotionally and physically trying time (Furuta et al 2014).

Another barrier to education is the limited time in one-to-one consultations, where many important issues need to be addressed, often resulting in information overload (Nolan 2009). However, this finding is linked to the pregnancy care model in the local settings of the study. In Aotearoa New Zealand, the continuity of care model should offer better opportunities for education on HDP (Grigg and Tracy 2013), but this idea needs to be further explored.

6.4 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 (Sauve et al 2008; Agarwal et al 2013). 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 (You et al 2012).

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 pregnant woman's comprehension of health information that is too complex to fully explain through text alone (Agarwal et al 2013). 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 Aotearoa New

Zealand, Rauemi Atawhai will prove to be a useful guide in developing education tools (Ministry of Health 2012).

6.5 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 pregnant women/people understand the implications and complications of HDP. Related to this is the importance of ensuring continuity of care in referral to secondary health services, which requires a three-way discussion about ongoing care and clinical responsibility between the lead maternity carer (LMC), the specialist and the pregnant woman/person (Ministry of Health 2012a). In line with the Health and Disability Commissioner Act 1994 and the associated patient code, such discussions should acknowledge and explain the pregnant woman's/person's rights (Health and Disability Commissioner 1996).

The Diagnosis and Management of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand: A clinical practice guideline (Te Whatu Ora 2022) 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 pregnant women/people's experiences.

It is vital that, throughout the pregnant woman/person's experience with health care services, health professionals fully inform them 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 to take a more 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 (Harrison et al 2003).

6.6 Location of care

Pregnant women/people with HDP may need to receive care away from their whānau/family, friends and usual support networks. This will often create additional stress for them (Clauson 1996; McCain and Deatrick 1994; Black 2007). Health professionals should make social services available, offer contacts with support groups and give the pregnant woman/person access to any travel and accommodation assistance they are eligible to through the appropriate health systems.

6.7 Demographic effects

Another important aspect of pregnant women/people'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') (Corbett et al 2014). 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 spouse/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 (Corbett et al 2014).

The findings from the Growing up in New Zealand study demonstrated that whether women engaged an LMC and whether they had a choice of health care provider varied depending on their demographics (Bartholomew et al 2015). Women who did not engage an LMC were more likely to be non-European, under 20 years old or over 40 years old, with poorer educational attainment or living in more deprived households. Women who did not have a choice of health care provider were also more likely to be non-European, under 20 years old or living in more deprived households (Bartholomew et al 2015). 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 those women in following specific advice in relation to hypertension in pregnancy.

7 Lifestyle (diet, physical activity, supplements)

Lifestyle – recommendations

Give the pregnant woman/person specific education around optimal weight gain. Refer to ***Eating and Activity Guidelines for New Zealand Adults*** **(Ministry of 2020)** and **Eating for Healthy Pregnant Women (Ministry of Health 2021)**.

Weak recommendation; very low-quality evidence

Do not offer multi-vitamins, vitamin C, vitamin E or other supplements, such as fish oil or magnesium for pregnant women/people at risk of preeclampsia.

Strong recommendation; moderate-quality evidence

Do not recommend salt restriction for pregnant women/people at risk of pre-eclampsia.

Strong recommendation; moderate-quality evidence

Do not recommend bed rest or restriction of physical activity for pregnant women/people at risk of pre-eclampsia.

Strong recommendation; very low-quality evidence

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

- lowering BP
- 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/people with hypertension.

7.1 Dietary salt restriction

The evidence on the effectiveness of salt restrictions is based mainly on the Cochrane systematic review of two trials involving 603 women (Duley et al 2005). These trials found salt restriction did not significantly reduce risk of pre-eclampsia (RR 1.11, 95% CI 0.46–2.66). 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.

7.2 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 women (Rumbold et al 2008) and a systematic review of 19,810 women (Conde-Agudelo et al 2011). The evidence did not demonstrate that antioxidants (vitamin C and/or vitamin E) significantly reduced the risk of pre-eclampsia (RR 0.73, 95% CI 0.51–1.06). In addition, evidence from five trials in this Cochrane review did not show benefit for reducing risk of preterm birth before 37 weeks' gestation (RR 1.10, 95% CI 0.99–1.22) or SGA babies (RR 0.83, 95% CI 0.62–1.11). Pregnant 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). However, a study (Rumbold et al 2015) comparing vitamin C alone and placebo found that those taking the supplement had a decreased chance of preterm premature rupture of membranes (RR 0.66, 95% CI 0.48–0.91).

Other RCTs not included in the Cochrane review showed similar findings, with no significant benefit for maternal or fetal outcomes for those pregnant women given vitamin C and E supplements compared with those given a placebo (Roberts et al 2010; Rumbold et al 2015). One large RCT (the VIP trial) showed possible harm from these supplements, associating them with low birthweight babies (Poston et al 2006). 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 (Wei et al 2013). However, the evidence is inadequate to draw reliable conclusions on the role of supplementation in preventing HDP. The available evidence is from one RCT of 400 women that combined vitamin D with calcium supplements (De-Regil et al 2012). This trial showed no significant benefit (RR 0.67, 95% CI 0.33–1.35) in preventing pre-eclampsia. 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) (Hyppönen et al 2013). The findings of the Hyppönen et al 2013 review 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. This study showed that this supplement had a significant benefit in preventing pre-eclampsia (RR 0.09, 95% CI 0.01–0.73) (Khatwa and el Kader

2012). 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 also reduce the risk of pre-eclampsia. Research shows folate biomarkers are low in women with pre-eclampsia (Singh et al 2015). 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) (Yang et al 2015).

This evidence statement does not cover iodine and magnesium supplementation because only two studies are available, and these are of very low quality (Rylander 2014; Borekci et al 2008).

7.3 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) (Meher et al 2005). 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 that 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) (Aune et al 2014). Researchers have suggested that physical activity stimulates placental angiogenesis and may have a role in reversing maternal endothelial dysfunction (Weissgerber et al 2004; Yeo and Davidge 2001). Large RCTs are needed to gather reliable evidence on the effect of physical activity on reducing the risk of hypertension in pregnancy.

7.4 Gestational weight gain

While beginning a pregnancy with a high BMI is a risk for HDP, targeted weight gain during pregnancy is associated with improved outcomes for both the pregnant woman/person and the baby regardless of the pregnant woman/person’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 (Ministry of Health 2014). 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 pregnant women 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) (Gaillard et al 2013).

A 2014 meta-analysis 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 (Ruifrok et al 2014). 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.

Another large retrospective population study of nulliparous women found that women with excessive weight gain (in relation to Institute of Medicine guidelines, Rasmussen and Yaktine 2009), 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) (Truong et al 2015).

High-sugar diets are also associated with increased risk of pre-eclampsia, whereas high fruit and vegetable diets are linked with a decreased risk (Brantsæter et al 2009; Borgen et al 2012). 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) (Thangaratinam et al 2012).

For consumer and health practitioner guidance and resources on gestational weight gain, see the Ministry of Health's *Guidance for Healthy Weight Gain in Pregnancy* (Ministry of Health 2014). That guidance recommends routine antenatal weighing. A recent pilot RCT showed this approach was acceptable to women and reduced excessive weight gain (Daley et al 2015).

7.5 Other factors

While recognising the limitations in current evidence, these evidence statements recommend that health professionals consider the pregnant woman/person's preferences when the professionals are advising on lifestyle and dietary interventions. Some pregnant women/people 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 that lead to appropriate gestational weight gain, it improves many maternal and neonatal outcomes (Ministry of Health 2014).

8 Aspirin prophylaxis

Aspirin prophylaxis – recommendations

Recommend low-dose aspirin (100 mg daily) in pregnant women/people with a major risk factor for developing pre-eclampsia and commence between 12- and 16-weeks' gestation.

Strong recommendation; moderate-quality evidence

Recommend the pregnant woman/person take aspirin at bedtime or in the evening.

Good practice recommendation

Consider stopping low-dose aspirin around 36 weeks' gestation.

Weak recommendation; very low-quality evidence

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 (Redman et al 1999; Roberts and Catov 2007).

8.1 Overall effect

The evidence of the effectiveness of low-dose aspirin is based mainly on the Cochrane systematic review of 46 trials involving 32,891 women (Duley et al 2007). 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). Furthermore, this approach reduced preterm births by 8%, SGA babies by 10% and perinatal deaths by 14%. The review observed no significant differences in 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) (Bergeron et al 2016).

8.2 Effect of risk prevalence

Although the evidence demonstrated that the difference based on maternal risk[2] 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) (Duley et al 2007).

In applying this evidence, it is important to note that the number needed to treat (NNT) is determined by the effect size and 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-eclampsia (Askie et al 2007).

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 studies (Etwel and Koren 2015).

8.3 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' gestation (Duley et al 2007). 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 weeks' gestation (Bujold et al 2010).

Two other meta-analyses of RCTs – one with three studies of 346 women (Villa et al 2013) and another with four studies of 392 women (Roberge et al 2012) – had similar findings. Other studies have shown that starting aspirin before 17 weeks' gestation reduced the risk for late-onset pre-eclampsia by 29%, supporting the practice of starting aspirin early in high-risk women (Moore et al 2015). In the trials reported in the systematic reviews and

[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 BP and no proteinuria, abnormal UADV scan, positive roll-over test, multiple pregnancies, a family history of severe pre-eclampsia and being a teenager, having renal disease or autoimmune disease.

meta-analyses, the earliest gestation at which women began taking low-dose aspirin was 12 weeks.

One moderate-quality systematic review of eight RCTs reported that low-dose aspirin (>75 mg/day) initiated before 11 weeks' gestation for pregnant women with a history of recurrent miscarriage, IVF, thrombophilia or anti-phospholipid syndrome did not decrease the risk of pre-eclampsia, gestational hypertension and other hypertensive disorders in later pregnancy (RR 0.52, 95% CI 0.23-1.17; p = 0.115) (Chaemsaithong et al 2020a). Reported results did not demonstrate increased risk of gastrointestinal bleeding.

Other large RCT evidence presented positive effect sizes. The ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Pre-eclampsia Prevention) trial reported that for women with a high risk of pre-term pre-eclampsia, low-dose aspirin (150 mg/day taken in the evening) initiated at 11–14 weeks' gestation reduced the incidence of pre-term pre-eclampsia compared with a placebo (OR 0.38, 95% CI 0.20-0.74; p = 0.004) (Rolnik et al 2017).

A large randomised control trial reported that, for high-risk women, taking a higher dose of low-dose aspirin (75 mg/day at bedtime) was effective at reducing later onset of pre-eclampsia, compared with a lower dose (25mg/day) or no low-dose aspirin ($\chi 2=10.237$; p=.001), and pre-term pre-eclampsia (<34 weeks' gestation) was much less likely than in the control group (27.5% of pre-eclampsia was pre-term in the control group compared with 3.8% of cases on the 75mg/day group) (Gu et al 2020).

Evidence regarding the association between early initiation of low-dose aspirin (before 13+6 weeks' gestation) and later onset of HDP remains limited. Few studies focus on first trimester initiation of daily low-dose aspirin (that is, systematic reviews and meta-analyses tend to analyse data by </> 16 weeks' gestation or </> 20 weeks' gestation). Few studies discussed aspirin ranges and impact on later onset of HDP.

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' 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 BP depended strongly on administration time (Ayala et al 2013). This study demonstrated that, compared with placebo, taking aspirin when waking up had no effect on BP, but taking it eight hours after waking up and, even more so, taking it at bedtime had a highly significant effect (p <0.001).

Further analysis combined those who took aspirin when they woke up with 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) (Ayala et al 2013). Other studies have had similar results (Hermida et al 2005). However, a recent systematic review on the topic suggests more research is needed in this area (Bem et al 2016).

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 (that is, 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 taking 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 (Henderson et al 2014).

8.4 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 (Duley et al 2007; Bergeron et al 2016). 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).

In a further subgroup analysis of doses of 60 mg, 75 mg, 100 mg and 150 mg per day, the NICE guideline development group demonstrated that 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) (NICE 2010). However, the reviewers acknowledge that this analysis may have been underpowered to detect a difference because it involved only a few studies.

8.5 Adverse effects and safety

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

Be cautious when giving aspirin to pregnant women/people:

- with asthma (up to 20% of asthmatics may be affected) (Morwood et al 2005). One study in a systematic review found that half of those who reacted did so at low doses of aspirin (≥80 mg) (Jenkins et al 2004)
- having anticoagulant treatment (for example, 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 (Tran-Duy et al 2015).

Gastric side effects of aspirin are usually associated with long-term use (that is, longer than normal pregnancy) and in higher doses. However, health professionals should monitor signs of gastritis or gastric ulceration. They should also advise all pregnant women/people 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' gestation (Duley et al 2007). 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.

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 (Bergeron et al 2016). Evidence for the safety of low-dose aspirin in the first trimester comes from a Cochrane systematic review examining effects on miscarriages (de Jong et al 2014). In this review, one RCT on adverse outcomes demonstrated no significantly higher risk of congenital malformations or bleeding with aspirin prophylaxis. 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 (Kozer et al 2002). 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 (Tran-Duy et al 2015; Bánhidy et al 2012). The absolute risk of gastroschisis in the general population is 5.16 per 10,000 live births (Srivastava et al 2009).

Most studies did not specify the dose of aspirin women took, and no analysis of outcomes based on dose was performed. The risks of low-dose aspirin in the first trimester are currently unknown.

8.6 Other factors

The cost-effectiveness of low-dose aspirin is indisputable for pregnant women/people 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 (Bujold et al 2010). Simulations of different models in the USA showed that a universal prophylaxis with aspirin was the most cost-effective approach (Werner et al 2015). 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 (Henderson et al 2014; de Jong et al 2014).

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

9 Calcium supplementation

Calcium supplementation – recommendations

Consider supplementation with calcium for pregnant women/people who have a major risk factor for pre-eclampsia, particularly those with low dietary intake of calcium, from booking to birth (1.5-2.0g oral elemental calcium is recommended).

Strong recommendation; moderate-quality evidence

Low calcium intake may cause high BP 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 (Belizán et al 1988; Hofmeyr et al 2014; Carroli et al 2010; Repke and Villar 1991).

9.1 Overall effect

The evidence showing that calcium supplementation can reduce the risk of HDP comes mainly from a Cochrane systematic review 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 (Hofmeyer et al 2014).

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. 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).

Another systematic review published in *BMJ Clinical Evidence* also observed that calcium supplementation is beneficial in pregnant women at risk of pre-eclampsia (Mackillop 2015). The evidence further demonstrated no overall effect on the risk of stillbirth, infant death or admission of the baby into intensive care (Hofmeyr et al 2014; Mackillop 2015). However, some researchers note that the moderate quality of evidence limits the usefulness of this intervention (Tang et al 2015).

9.2 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) and those at high risk (RR 0.22, 95% CI 0.12–0.42). 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 (Hofmeyr et al 2014).

9.3 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 an NICU (Hofmeyer et al 2014). 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; and again, further research in this area is needed. The World Health Organization (WHO) currently recommends starting at 20 weeks' gestation and continuing until birth, but ongoing research, such as the CAP (WHO Department of Reproductive Health Research, Instituto de Efectividad Clínica Sanitaria Buenos Aires 2016) and AMCAL (Federal University of São Paulo nd) 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.

9.4 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 compared with 6) (Hofmeyr et al 2014).

One study in the Republic of the Gambia noted rebound postnatal bonepregnant izationn following calcium supplementation in women with low intake (Hofmeyr et al 2014; Jarjou et al 2010). However, the quality of this evidence was low. It also noted that 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 (Repke et al 2002; Mackillop 2015; Imdad et al 2011).

9.5 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 seven (Hofmeyr et al 2014).

9.6 Other factors

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

- Researchers note high-dose calcium tends to be unpalatable, making thepregnant woman's/person's preferences and likely compliance an important consideration, and other formulations are available.
- The calcium content of any other vitamin supplements the pregnant woman/person is taking should also be considered.

10 Antihypertensive medicines

Antihypertensives – recommendations

Urgently treat all pregnant women/people with severe hypertension (dBP ≥110 mmHG or sBP ≥160 mmHg) with antihypertensives to acutely lower blood pressure.

Strong recommendation; low-quality evidence

Consider antihypertensives for pregnant women/people with gestational hypertension (dBP ≥90 mmHG or sBP ≥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 medicine in the context of resource availability, the local health care setting and the condition of the pregnant woman/person.

Strong recommendation; very low-quality evidence

Provide information on antihypertensive medicines, symptoms of pre-eclampsia, and when and how to report symptoms. The information should be in plain English or a language the pregnant woman/person understands if English is not the first language.

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

BP 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 BP approximately normal. Hypertension can be produced by vasoconstriction (increased vascular resistance) or increased cardiac output (Bosio et al 1999; Easterling et al 1990). Antihypertensives work by causing vasodilation (such as calcium channel blockers) or by reducing cardiac output (for example, by reducing heart rate, such as with beta-blockers). Reducing cardiac output or BP can potentially compromise the fetus (Easerling 2014).

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 medicine may vary

in its effects on the fetus. For example, some beta-blockers are associated with intrauterine growth restriction (IUGR) whereas labetalol have the least impact. In contrast, calcium channel blockers may be associated with reduced IUGR, but they are also linked with fetal tachycardia (Giannubilo et al 2012).

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 woman and fetus benefit (Easterling 2014).

10.1 Categories of hypertensive medicines for pregnancy

Calcium channel blockers and beta-blockers are the medicines of choice in pregnant women/people for BP control. Research shows they are safe and effective in pregnancy. However, no strong evidence suggests that one class of antihypertensive medicines is better than another (Abalos et al 2014). Methyldopa (an indirect agonist for alpha2-adrenergic receptors) is another commonly used medicine for hypertension in pregnancy. However, it is slower to act than some other calcium channel blockers or beta-blockers (Lowe et al 2015).

Contraindicated: Pregnant women/people should not normally use ACE inhibitors and angiotensin receptor blockers in pregnancy because they potentially have harmful fetal effects (see ‘Adverse effects and safety’ under 10.4 HELLP syndrome below). These evidence statements exclude them from the discussion of evidence and reference to any hypertensive class/medicine.

10.2 Antihypertensive medicines for the management of hypertension in pregnancy

Reducing the risk

The evidence for the effect of antihypertensive medicines is based on a Cochrane review of 49 trials (4,723 women) and is of moderate to low quality (Abalos et al 2014). In the Abalos et al 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). However, the analysis also suggests that treatment with antihypertensive medicines does not reduce the risk of developing pre-eclampsia (RR 0.93, 95% CI 0.80–1.08) or any other maternal or fetal outcome. On the other hand, when antihypertensives were assessed in different types of mild to moderate hypertension, they were found to be effective at reducing the risk of severe hypertension and pre-eclampsia (Abalos et al 2014).

Comparisons of medicines

There is no clear evidence suggesting that one class of antihypertensive medicine is better than another, and evidence shows no significant differential effects (Abalos et al 2014). When compared with no treatment, calcium channel blockers did not reduce the risk of developing pre-eclampsia or severe hypertension, but beta-blockers significantly reduced the risk of developing pre-eclampsia and severe hypertension, while methyldopa reduced the risk of developing severe hypertension.

However, the Cochrane review (Abalos et al 2014) 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). There were no significant differences between any outcomes when beta-blockers or glyceryl trinitrate were compared with calcium channel blockers.

Target blood pressure

These evidence statements do not recommend aggressively normalising BP. The evidence from another Cochrane review (two trials, 256 women) indicates that in pregnant women with mild to moderate hypertension, very tight control of BP (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 an NICU RR 0.77, 95% CI 0.45–1.31) (Nabhan and Elsedawy 2011). The Control of Hypertension in Pregnancy Study (CHIPS), published since the Cochrane review, found that while tight control (target dBP, 85 mmHg) did not affect outcomes for infants, severe hypertension (≥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 ($p < 0.001$) (Magee et al 2015).

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 SGA babies. The researchers have attributed this finding to the effect of the hypertensive disease rather than the antihypertensive medicine (Orbach et al 2013; Duley et al 2013). 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 compared with 15.5%, $p < 0.05$) (Giannubilo et al 2012), and the second compared any beta–blocker with methyldopa (AOR 1.95, 95% CI 1.21–3.15) (Xie et al 2014).

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 for mild to moderate hypertension in pregnant women and the choice of medicine for such treatment must be based on interpretation of current evidence, potential adverse effects and clinical experience and judgment. It must also be specific to the individual woman and the effects on woman and baby (Orbach et al 2013).

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

- All antihypertensive medicines appear to be equally effective for maintaining BP 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’ under 10.4 HELLP syndrome below).
- Calcium channel blockers (for example, 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 compared with labetalol.
- Beta-blockers (for example, labetalol) have conventionally been the first-line use for BP control in pregnancy, but evidence supporting their use is of low quality. 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.

10.3 Antihypertensive medicines for managing severe hypertension in pregnancy

Reducing the risk

It is commonly accepted that using antihypertensives 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 in using 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 single antihypertensive medicine is more effective or safer than another (Duley et al 2013).

However, the evidence from the Duley et al Cochrane review demonstrated that women allocated calcium channel blockers were less likely to have persistent high BP compared with those allocated hydralazine (six trials, 313 women; 8% compared with 22%, RR 0.37, 95% CI 0.21–0.66). Alternative hypertensive medicines 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 –0.11 (–0.20 to –0.02), NNTH 7 (5–69)) (Lowe et al 2015). Studies have found no significant differences in maternal or fetal outcomes with the different antihypertensive medicines (Duley et al 2013; Firoz et al 2014).

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% compared with 9%; RD 0.26; 95% CI 0.07–0.46, one trial, 64 women) (Firoz et al 2014). When studies compared short-acting nifedipine with intravenous hydralazine in pregnancy, they observed no significant difference in effectiveness (achievement of target BP (84% [nifedipine] compared with 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% compared with 55%, RR 0.97, 95% CI 0.50–1.88; four trials, 246 women) (Firoz et al 2014).

In the Firoz et al 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 medicines (RR 0.05, 95%CI –0.03 to 0.12) or other adverse maternal and fetal outcomes. In severe hypertension, the risk of persistent high BP was lower for a calcium channel blocker (nimodipine) compared with magnesium sulphate (two trials, 1,683 women; 47% compared with 65%, RR 0.84, 95% CI 0.76–0.93). However, these two medicines did not differ significantly in changing the risk of developing eclampsia (Duley et al 2013).

Number needed to treat

No statistics on NNT was identified in the literature for poor maternal outcomes (for example, 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 medicine researchers compared it with (Magee et al 2000).

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 medicines in managing severe hypertension on the availability of the medicines, their own experience, the pregnant woman'/person's condition, that woman/person's compliance with medicine administration and the local health care setting.

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 was identified. In this situation, the information available is based on expert opinion, usually provided in clinical guidelines. Box 1 sets out suggested treatment regimens for the acute management of severe hypertension in the ACOG (Task Force on Hypertension in Pregnancy 2013) and SOMANZ (Lowe et al 2015) guidelines.

Box 1: Antihypertensive agents for acute lowering of severe hypertension Start one of these regimens in all pregnant women/people with severe hypertension (dBP110 or sBP ≥160 mmHg).
1BLabetalol 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
0BNifedipine Initially 10 mg (use immediate release capsules) Onset of action: 30–45 minutes Onset of maximum effect: 30 minutes Repeat: after 30–45 minutes (if needed) Maximum: 80 mg daily
2BHydralazine 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 the first IV hydralazine dose (usually 200–300 mL)

10.4 HELLP syndrome

The evidence does not demonstrate any reduction in the risk of developing HELLP through using antihypertensive medicines (Duley et al 2013).

Adverse effects and safety

Angiotensin converting enzyme (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 medicines (for example, 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 (Cooper et al 2006; Steffensen et al 1998). 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) (Cooper et al 2006). 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 (Bullo et al 2012). 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 (Pucci et al 2015). Therefore, a woman/person planning to become pregnant should discuss switching to an alternative hypertensive with their specialist in anticipation of becoming pregnant. When pregnancy is confirmed for any woman/person taking an ACE inhibitor, their general practitioner (GP) or an obstetric consultant should prescribe them an alternative medicine (following the *Guidelines for Consultation with Obstetric and Related Medical Services, Referral Guidelines*, Ministry of Health 2012).

The evidence from the Cochrane reviews on using antihypertensive medicines in mild to moderate and severe hypertension also did not show any significant differences in maternal or fetal outcomes in the various antihypertensive agents (Abalos et al 2014; Duley et al 2013). However, a cohort study of 1,418 women who reported using antihypertensive medicines in early pregnancy found an increased risk of infant cardiovascular defects (OR 2.59, 95% CI 1.92–3.51) (Lennestål et al 2009). Stillbirth rate also increased (RR 1.87, 95%CI 1.02–3.02), again without any clear differences between the medicine used (Lennestål et al 2009). 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 for children born to women who were treated or not treated for their hypertension (Easterling 2014).

The limitations in evidence suggest that clinical judgement must consider adverse effects and contraindications of specific medicines. For instance, one side effect of methyldopa is depression, which makes it perhaps not the best choice in long-term antenatal or postpartum control of hypertension (Lowe et al 2015). Also in the postpartum period, hypotension may be a side effect in the neonate of the breastfeeding woman (NICE 2010).

10.5 Postpartum

The evidence for antihypertensive treatment postpartum comes from a Cochrane review of nine RCTs (838 women) (Magee and von Dadelszen 2013). 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. In this review, use of additional hypertensives (comparing 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 medicines were well tolerated, but the trials were not consistent in their effects. 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 (Magee and von Dadelszen 2013).

As it has been demonstrated that peak postpartum BP 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 BP unless they ensure the woman has close follow-up (Magee et al 2014).

Research has produced weak evidence on the compatibility of antihypertensive medicines 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 medicines appear to be safe for the baby and the benefits of breastfeeding outweigh potential risks to the baby of transferring antihypertensive medicines in breast milk (NICE 2010). 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 (National Collaborating Centre for Women’s Children’s Health 2010).

11 Maternal and fetal monitoring

Antenatal monitoring recommendations

For pregnant women/people with hypertension, refer to an obstetric specialist for a consultation and full assessment. The specialist should make a plan of who is going to carry out the ongoing care and monitoring of the woman/person and their baby in conjunction with the woman/person and their LMC.

Strong recommendation; very low-quality evidence

For pregnant women/people with hypertension who are managed as outpatients, base the frequency of additional antenatal appointments (from the conventional appointment schedule) on each woman/person's individual needs, the severity of her/their condition and their preferences.

Strong recommendation; very low-quality evidence

For a pregnant woman/person presenting with features of pre-eclampsia, refer urgently (same day) to an obstetric specialist and a transfer of care (referral code 4022). Consider offering inpatient management. Consider the practical (social and economic) implications of inpatient care from the woman's/person's perspective.

Strong recommendation; very low-quality evidence

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

Good practice recommendation

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

Good practice recommendation

Pregnant women/people with a major risk factor for pre-eclampsia should have uterine artery Doppler studies performed at their 20-week anatomy scan. The results of such assessments can be used to plan the schedule for serial growth assessment.

Good practice recommendation

Make a clear management plan for all pregnant women/people with HDP. The plan should include clinical responsibilities and reflect the pregnant woman/person's preferences.

Good practice recommendation

Postnatal monitoring recommendations

Carefully monitor pregnant women/people for increasing hypertension postpartum. Blood pressure frequently increases about three to five days after birth. Continue to monitor BP at routine postnatal assessments.

Strong recommendation; very low-quality evidence

Continue to observe strict fluid balance in pregnant women/people with severe pre-eclampsia.

Weak recommendation; low-quality evidence

Monitor until all signs of pre-eclampsia (including pre-eclampsia bloods) return to normal but beware of post-partum severe features of pre-eclampsia or eclampsia.

Strong recommendation; high-quality evidence

Most commonly used antihypertensive medicines appear to be safe for babies. The benefits of breastfeeding outweigh potential risks to babies of transfer of antihypertensive medicines in breast milk.

Good practice recommendation

Pregnant women/people with HDP are at higher risk of venous thromboembolism. Assess the need for preventive treatments, using a recognised risk assessment tool.

Good practice recommendation

This evidence statement has two main parts: maternal monitoring and fetal monitoring. Support for monitoring pregnant women/people with HDP comes from the evidence of high maternal and fetal adverse outcomes and the rapid progress to severe disease. No evidence on the protocols of maternal monitoring and their effects on the maternal and fetal outcomes was identified.

11.1 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 (Barton et al 2001; Saudan et al 1998; Solomon and Seely 2011). Studies have demonstrated that 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 (Li et al 2014). 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 HDP (Lowe et al 2015; Magee et al 2014; NICE 2010). 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 health care services (Knuist et al 1998). No RCT was found on a particular schedule or

place for maternal monitoring, but expert opinion suggests customising modalities and schedules for monitoring the individual woman (McCarthy and Kenny 2015).

The current parameters of maternal monitoring focus on measuring BP, proteinuria, symptoms of pre-eclampsia, tests of systemic functions (hepatic, renal and coagulation) and symptoms indicative of interventions for birth (NICE 2010; Task Force on Hypertension in Pregnancy 2013; Knuist et al 1998).

Blood pressure

The device used for and technique of BP 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 (Waugh et al 2002). 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) (Lan et al 2014). Studies using calibrated automated devices tested in pregnant women show results comparable with those of mercury sphygmomanometers (Brown et al 2012).

In view of the evidence, clinical practice guidelines and the ISSHP statement, this evidence statement recommends that any automated devices used for BP measurement should have demonstrated reliability for BP measurement in pregnant women (Tranquilli et al 2014).

Blood pressure – device

It is recommended that Korotkoff phase 1 be used to measure sBP and Korotkoff 5 to measure dBP (Shennan et al 1996). The sBP is accepted as the first sound heard (K1) and the dBP as the disappearance of sounds completely (K5). Where K5 is absent, accept K4 (muffling).

Correct cuff size is important for accurately recording BP. 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 (Pickering et al 2005; Reinders et al 2006). This practice helps to minimise overdiagnosis of hypertension during pregnancy as a cuff that is too small will overestimate BP. Deflate the cuff at a rate of ≤2 mm per second as rapid deflation leads to underestimation of the sBP (Reinders et al 2006; Chancellor and Thorp 2008).

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

women (Stone et al 1995). Randomised controlled trials offer no evidence on the effectiveness of alternative modalities of BP measurement during pregnancy (Bergel et al 2002). However, evidence from observational studies suggests that using 24-hour ambulatory BP monitoring (ABPM) is the ideal way of making the diagnosis (Head et al 2012; Moser et al 2012; Raio et al 2015). Some observational studies have shown that ABPM correlates better with proteinuria than conventional sphygmomanometry and is a better predictor of hypertensive complications and that it is effective in differentiating white coat hypertension (Head et al 2012; O'Brien et al 2001). However, the availability and cost of ABPM limit the extent to which it can be used; so this evidence statement suggests using the conventional BP measurement at a clinical setting measured at least four hours apart (Magee et al 2014).

Blood pressure – technique

The evidence for the optimum technique for BP measurement is also limited, however. The current opinion is that BP should be measured with the pregnant woman/person rested and seated at a 45-degree angle with the arm at the level of the heart. A study of 5,434 pregnant women has demonstrated that the variation in BP between arms is usually less than 10 mmHg (inter-arm difference of at least 10 mmHg in sBP was observed in 8% of pregnant women; for dBP, a similar variation in diastolic was observed in 2% of pregnant women) (Poon et al 2008). In labour, BP measurement in the lateral position is considered to be appropriate, but researchers have noted that measuring BP on the right arm with the woman in the left lateral position may give falsely lower recordings, as may measuring while the woman is in a supine posture (on their back) (Lowe et al 2015; Task Force on Hypertension in Pregnancy 2013).

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 (Meher et al 2005; Sibai 2003). Furthermore, the evidence from observational studies shows that the prognostic value of home BP monitoring is equal to or higher than that of office BP monitoring (Parati et al 2010). 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 interventions (Tuffnell et al 1992). An Australian study showed that using telemedicine in high-risk pregnancies increased the number of appointments the pregnant woman kept and permitted timely referrals, as well as still permitting many pregnant women to deliver closer to their hometowns (Ivey et al 2015).

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 if the dipstick test is positive (see section 3: Classifications and clinical definitions above).

Many studies have compared the consistency of a protein:creatinine test with 24-hour urinary protein. A systematic review of protein tests in hypertensive pregnant women found protein:creatinine to be a simple and practical indicator of proteinuria and points out the disadvantages of 24-hour urine collection, including delayed diagnosis and inaccuracy (Côté et al 2008). It also mentions that the National Kidney Foundation in the USA now recommends spot protein:creatinine tests (instead of 24-hour urine collection) to diagnose proteinuria in most situations (Vassalotti et al 2007). Once proteinuria is established, this evidence statement does not recommend monitoring for severity as studies have not found that its level of severity predicts worsening of the disease (Tranquilli et al 2013; Homer et al 2008; Thornton et al 2010).

Monitoring the systemic functions

This evidence statement recommends testing blood for renal function, liver function and platelet count at the time of diagnosis of new proteinuria or when a woman's BP suddenly increases (Lowe et al 2015; Magee et al 2014; McCarthy and Kenny 2015).

Several studies have shown that women with pre-eclampsia are at higher risk of venous thromboembolism (VTE) (for example, 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 VTE postpartum (van Walraven et al 2003).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 (Sultan et al 2013).

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 (Parunov et al 2015). In light of this evidence, health care professionals should evaluate the need for postnatal preventive treatments for VTE using a recognised pregnancy VTE risk assessment tool (McLintock et al 2012), such as those described in the Royal College of Obstetricians and Gynaecologists' *Thrombosis and Embolism during Pregnancy and the Puerperium Green-top Guideline* (RCOG 2015).

Monitoring the symptoms of pre-eclampsia

Common advice for pregnant women/people at risk of, or with, HDP 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) (Poon et al 2008). 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 (Black and Morin 2014). 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) (Black and Morin 2014). 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 (von Dadelszen et al 2011). 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) (von Dadelszen et al 2011).

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 (von Dadelszen and Magee 2014). This miniPIERS model is limited to demographics, symptoms and signs (parity (nulliparity compared to parity), gestational age on admission, headache/visual disturbances, chest pain / dyspnoea, vaginal bleeding with abdominal pain, sBP, 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 ≥25% to define a positive test classified women with 85.5% accuracy (von Dadelszen and Magee 2014). 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 BP 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 (Lowe et al 2015; Magee et al 2014; Sibai 2012). This evidence statement 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 assessing the fetus every two to three weeks. It also advises that women monitor fetal movements and report immediately if they develop vaginal spotting, abdominal pain or uterine contractions (Lowe et al 2015; Magee et al 2014). The frequency of monitoring in severe cases depends on the severity of the conditions (von Dadelszen and Magee 2014).

Postpartum monitoring is also critical in women with HDP, 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 (Sibai 2012). Further evidence shows that BP 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/people 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 to enable their BP to be monitored and relevant laboratory investigations to be conducted (NICE 2010). Using nonsteroidal anti-inflammatory medicines (NSAIDs) postpartum involves a theoretical risk. Avoiding using them for pain relief may help control persistent hypertension, as these medicines may increase BP and adversely affect kidney function. One study, however, found that women who had severe HDP and took NSAIDs did not experience a difference in the average mean arterial pressures postpartum (Wasden et al 2014).

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 (Lowe et al 2015; Sibai 2003). The benefit of admitting pregnant women/people for this purpose is that it is possible to individualise appropriate assessments of maternal and fetal status and makes it easier for those involved in the pregnant woman's/person's care to have three-way communication and discussion. As such, you need to consider the criteria of the *Referral Guidelines* (Ministry of Health 2012) for pregnant women/people 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 (Magee et al 2014). For this reason, in non-severe cases, the place for monitoring maternal condition needs to consider the location of the pregnant woman/person in relation to an appropriate facility, resources available and the woman's/person's preference for complying with monitoring requirements.

11.2 Fetal monitoring

Although HDP 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 for these aspects (Gruslin and Lemyre 2011). 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 (Lowe et al 2015; Magee et al 2014; NICE 2010; Task Force on Hypertension in Pregnancy 2013; McCowan et al 2014).

Fetal monitoring in HDP involves assessing fetal activity including fetal growth, movement, amniotic fluid volume, biophysical profile, fetal heart rate and cardiovascular parameters (Gruslin and Lemyre 2011; Bolte et al 2001). It also involves evaluating placental function, transport and perfusion.

Assessing fetal growth

SGA is defined in the [3]New Zealand Maternal Fetal Medicine Network (NZMFMN) *Guideline for the Management of Suspected SGA Singleton Pregnancies and Infants after 34 weeks' Gestation* as an infant with birthweight that is less than the 10th birth weight centile or a fetus with an estimated fetal weight on a customised growth chart less than 10th customised centile for gestation (McCowan and Bloomfield 2014). FGR1 has considerable overlap with SGA but is more difficult to define as not all growth-restricted infants are SGA.

IUGR 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 (McCowan and Horgan 2009).

It is imperative to identify any growth issues early: one study showed that infants that were not identified as being SGA before birth were at a four times greater risk of adverse fetal outcome (OR 4.1, 95% CI 2.5–6.8) (Lindqvist and Molin 2005). In practice, at the community level, health professionals often use fetal growth to assess symphysio-fundal (SF) height, but SF height has a high false-positive rate for detecting 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 (Pay et al 2015). Evidence from an observational study demonstrated that the 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)

[3] At the time of publication an updated national guideline: Small for gestational age and fetal growth restriction in Aotearoa New Zealand is being developed. Once published the Diagnosis and Treatment of Hypertension and Pre-eclampsia in Pregnancy in Aotearoa New Zealand and evidence and evidence statements will be updated to reflect the new guidance.

chart – was compared with a record in clinical notes but not plotted on a chart (24.8%) (Roex et al 2012).

However, another RCT demonstrated that fetal growth assessment with ultrasound has a higher sensitivity and specificity for detecting FGR compared with SF height (sensitivity, 100% compared to 42.86%; specificity, 92.62% compared to 85.24%) (Haragan et al 2016). 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 SGA and FGR associated with HDP, this evidence statement recommends using ultrasound to assess serial fetal growth.

This evidence statement further suggests that pregnant women at high risk of SGA (including chronic and pregnancy-induced hypertension) should have serial growth scans scheduled as part of their secondary health care pathway. For women identified as being at high risk of pre-eclampsia, conducting an uterine artery Doppler assessment at 20–24 weeks' gestation 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' gestation (Cnossen et al 2008; Giordano et al 2010). While this assessment has limited predictive value even in high-risk populations, a reassuring uterine artery Doppler study result may indicate that fewer ultrasound evaluations can be performed during the pregnancy, while an abnormal outcome would suggest more intensive surveillance is required (Chien et al 2000; Axt-Fliedner et al 2005). See also ultrasound markers in section 5: Prediction – biomarkers and ultrasonographic markers.

Asesing fetal status and distress

Fetal movement

Common advice is for caregivers to monitor fetal movement, and often use this spontaneously to assess the baby's wellbeing. However, no specific evidence has been identified in relation to HDP.

A population-based study of 691 women demonstrated that low maternal awareness of fetal activity was associated with an increased risk of having a SGA baby (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) (Saastad et al 2008). 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 Mangesi et al 2015). The findings indicated that 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). 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 (Mangesi et al 2015). Similarly, there is insufficient evidence on the management strategies for decreased fetal movements, such as vibroacoustic stimulation or mock stimulation for women whose babies are thought to be at risk of compromise for various reasons (Hofmeyr and Novikova 2012).

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 breathing, and ultrasound assessment of liquor volume with or without assessment of the fetal heart rate.

A Cochrane review of five trials (2,974 women) does not support using BPP as a test of fetal wellbeing in high-risk pregnancies (Lalor et al 2008). 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 5 minutes (RR 1.27, 95% CI 0.85–1.92). 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 (Payne et al 2010). This 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 pregnant women with pre-eclampsia.

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 pregnant women/people with HDP.

Studies show that 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 (Gruslin and Lemyre 2011). 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 (Williams et al 2003). 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.

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 FGR and pre-eclampsia (particularly early onset disease) (Gruslin and Lemyre 2011).

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 (Alberry and Soothill 2007).

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 rather than the first trimester (Cnossen et al 2008). 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 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 (Cnossen et al 2008).

Umbilical artery Doppler

A Cochrane review reported that umbilical artery Doppler ultrasound in high-risk pregnancies (including HDP) 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). However, due to the low quality of the current evidence, Alfirevic et al 2013 recommended interpreting results with some caution.

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 PI; 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 (Orabona et al 2015).

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 one group being assessed twice a week and the other assessed fortnightly (both groups had growth assessed fortnightly) (Grivell et al 2012). 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). Some evidence indicates that fetal surveillance in a day assessment setting could be as effective as inpatient surveillance when BP is well controlled and if women have no other complications (Abramovici et al 1999; Turnbull et al 2004).

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– and their impact on timing of birth. While the difference in the proportion of infants surviving without neurological impairment was not significant in relation to timing of birth, the researchers suggested that using late changes in DV might improve 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' gestation) (Lees et al 2015).

Summary

In summary, there is limited evidence from high-quality studies to inform best practice for fetal surveillance modalities or regimens for managing pregnant women/people with HDP. However, the high risk of intrauterine FGR and adverse fetal outcomes in pregnant women/people with hypertension has prompted expert opinion to include fetal surveillance in the clinical management of these women/people. 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 (Lowe et al 2015; NICE 2010; Task Force on Hypertension in Pregnancy 2013). In severe forms of the disease, much closer surveillance is appropriate, which includes more frequent umbilical artery Doppler evaluations and CTGs (Gruslin and Lemyre 2011; Sibai et al 2007).

Where they identify SGA or FGR, health professionals may look for guidance on management from the NZMFMN's *Guideline for the Management of Suspected SGA Singleton Pregnancies and Infants after 34 weeks' Gestation* (McCowan et al 2014). A national small for gestational age and fetal growth guideline is under development, and once finalised, this guideline will be updated to incorporate any changes related to HDP.

11.3 Other factors: pregnant women/people's preferences and local setting

Pregnant women/people's preferences are an important aspect that need to be considered when health professionals are advising them about maternal and fetal surveillance. The advice needs to be clear on the choices available to pregnant women/people and benefits and risks around the surveillance modalities; and the advice needs to be individualized to each pregnant woman/person's situation. This is important as some studies have shown that the support pregnant women/ received from staff and labour companions is more important than the type of monitoring used (Garcia et al 1985; Killien and Shy 1989).

Also the maternity care model in Aotearoa New Zealand needs to be considered 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.

12 Magnesium sulphate

Magnesium sulphate – recommendations

In pregnant women/people with eclampsia, recommend administering magnesium sulphate to help prevent seizures, unless contraindicated.

Strong recommendation; very high-quality evidence

In pregnant women/people with severe pre-eclampsia, recommend administering magnesium sulphate to reduce the risk of eclampsia.

Strong recommendation; high-quality evidence

Recommend administering magnesium sulphate in a setting with one-on-one midwifery 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 pregnant woman/person to a higher-level health care facility.

Strong recommendation; low-quality evidence

Consider continuing magnesium sulphate for 24 hours following birth or 24 hours after the last seizure, whichever is the later.

Strong recommendation; very low-quality evidence

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

Good practice recommendation

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

Good practice recommendation

Understanding is limited about the mechanism of action for magnesium sulphate in preventing and treating eclamptic seizures (Okusanya et al 2012). The evidence indicates that this medicine treats eclampsia through its effect on several cardiovascular and neurological functions and by altering calcium metabolism (Euser and Cipolla 2009; Sadeh 1989; Goldman and Finkbeiner 1988). 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 (Belfort and Moise 1992; Abad et al 2015) and act as a cerebral anticonvulsant (Euser and Cipolla 2009).

12.1 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 (Duley et al 2010a). However, the reduction in the risk of maternal death was not significant (RR 0.54, 95% CI 0.26–1.10) (Duley et al 2010a). 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 placebo (Duley et al 2010a).

As a treatment

Another Cochrane review of several trials (1,369 women with eclampsia) compared the effectiveness of magnesium sulphate and diazepam (Duley et al 2010b). It demonstrated that 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). Similar findings on the effectiveness of magnesium sulphate compared with diazepam came from a systematic review of two studies among postpartum women (Vigil-De Gracia and Ludmir 2015).

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) (Duley et al 2010b). Another finding was that magnesium sulphate is superior to phenytoin in reducing the risk of eclampsia (Duley et al 2010a).

Effect of severity and timing in preventing eclampsia

Evidence from the Belfort and Moise (1992) Cochrane review 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).

A systematic review of published reports showed that a significant number of eclamptic women had either normal BP or mild-to-moderate hypertension immediately before seizure, further suggesting its benefit for prevention irrespective of the severity of pre-eclampsia (Girsen et al 2015). 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) (Belfort and Moise 1992). 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 compared to 16.6 ± 9.3 days, log-rank test, p = 0.021) (Ueda et al 2016). Its findings were similar in women with severe pre-eclampsia occurring before 28 weeks' gestation (n = 11, 4.5 ± 5.2 compared to 13.2 ± 6.8 days, log-rank test, p = 0.035). The study found no significant differences in major adverse outcomes (Ueda et al 2016.

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 (The Eclampsia Trial Collaborative Group 1995; Altman et al 2002). 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) (Duley et al 2010c). 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). 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 wide (Duley et al 2010c).

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 (Duley et al 2010c). Other small RCTs comparing shorter durations (4 hours, 6 hours and 12 hours) (Sahu et al 2015; Anjum et al 2015; Kashanian et al 2015) 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.

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) (Pratt et al 2015). 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) (Pratt et al 2015).

Adverse effects and safety

The Cochrane review (Duley et al 2010a) 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.

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% compared to 12%, p < 0.001). However, the difference in length of stay in an NICU was not significant (median 5 (range 2–91) compared to 6 (range 3–15), p = 0.5) (Girsen et al 2015).

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) (Duley et al 2010a), these effects may still have clinical significance. 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 (Duley 1996). The literature does not explore the impact of the frequency of monitoring these signs, while studies seem to apply it somewhat arbitrary.

Because of the rare possibility of toxicity, the magnesium sulphate maintenance dose should only be administered in settings where one-on-one care, close monitoring and resuscitation/reversal medications (calcium gluconate) are available. 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 (for example, epilepsy). This evidence statement suggests that an IM loading dose of magnesium sulphate before transfer to a referral facility may be beneficial for pregnant women with severe disease (WHO 2011) and for those where IV access could be difficult to obtain.

Numbers needed to treat

From the Duley et al 2010a Cochrane review and particularly the Magpie trial (Altman et al 2002), 90 women were the NNT with magnesium sulphate to prevent one woman from having a seizure in the international population. However, in Aotearoa New Zealand, a country with a high gross national income, the NNT is 324 (Simon et al 2006). In terms of number needed to harm (NNTH) for the woman, 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 of achieving generalisable results.

Note: Magnesium sulphate is also used for neuroprotection of the premature neonate (<30 weeks), in which case it is administered to the pregnant woman/person in the 24 hours before birth. If a pregnant woman/person is having magnesium sulphate for pre-eclampsia, they do not need an additional dose for neuroprotection. There are no Aotearoa New Zealand guidelines, ratified by the Ministry of Health (Ministry of Health 2016), 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* (Antenatal Magnesium Sulphate for

Neuroprotection Guideline Development Panel 2010). These guidelines were developed in consultation with a multidisciplinary team from Australia and Aotearoa New Zealand.

12.2 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 (Simon et al 2006). 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 (Duley et al 2010a; Pratt et al 2015).
- 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 (WHO 2011), particularly if there is a significant delay before transfer. This may be given IM (see magnesium sulphate protocol).

13 Timing of birth

Timing of birth – recommendations

For pregnant women/people 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 pregnant women/people with a low risk of adverse outcomes, consider expectant management. Early term birth (37- and 38-weeks' gestation) is associated with poorer neonatal and childhood outcomes compared with babies born at full term (39 to 40+6 weeks' gestation). Unless there is an evidence-based indication supporting earlier planned birth, continue expectant management to 39 weeks' gestation or more.

Strong recommendation; moderate-quality evidence

For pregnant women/people 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 pregnant woman/person, their LMC and the obstetric team should negotiate the timing.

Strong recommendation; moderate-quality evidence

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

Before 34+0 weeks: Plan an expectant approach. A clear plan should be discussed and agreed with the pregnant woman/person and clearly documented, including level of monitoring and thresholds to plan birth if the pregnant woman's/person's and/or fetus' condition deteriorates. Consider inpatient management.

Strong recommendation; low-quality evidence

At 34+0 to 36+6 weeks: Plan an expectant approach. Offer induction of labour if maternal or fetal indications support birth. Consider inpatient management.

Strong recommendation; moderate-quality evidence

Discuss with the pregnant woman/person and their whānau the risks and benefits for planned early birth (reducing maternal adverse outcomes) and expectant management (reducing need for neonatal intensive care unit admission and associated with improved early childhood developmental outcomes).

Good practice recommendation

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 pregnant woman/person, their LMC and the obstetric team.

Weak recommendation; low-quality evidence

For pregnant women/people with severe/unstable pre-eclampsia

Pre- and periviable gestation: Manage the condition in a tertiary setting in consultation with neonatology, the pregnant woman/person and their whānau and maternal fetal medicine if required.
See also the New Zealand Consensus Statement on the care of mother and baby(ies) at periviable gestations (Newborn Clinical Network 2019).

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, if <30 weeks, also administer magnesium sulphate for fetal neuroprotection.

Strong recommendation; moderate-quality evidence

Plan to manage expectantly until the course of antenatal corticosteroids is complete and the pregnant woman/person has been transferred to a centre with the appropriate level of neonatal care, but expedite birth if the maternal or fetal condition deteriorates.

Good practice recommendation

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

Strong recommendation; low-quality evidence

For pregnant women/people with HELLP

Any gestational age: Recommend birth after stabilising the pregnant woman/person and after they have completed a course of corticosteroids (≤34+6 weeks) and magnesium for neuroprotection (if <30 weeks) (unless there is maternal or fetal deterioration and if time permits).

Strong recommendation; moderate-quality evidence

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 pregnant woman/person's condition (expectant management) with the aim of improving the outcomes for the fetus. There are risks and benefits for both expectant management and immediate birth depending on severity of hypertensive disorder, gestational age at diagnosis and the competing interests of optimising maternal wellbeing and fetal maturity.

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 birth within 24 hours if induction was contraindicated) with expectant monitoring in pregnant women with non-severe HDP. A Cochrane systematic review of four RCTs of 425 women at 24–34 weeks' gestation and the MEXPRE Latin study (a RCT of 267 women 28–33 weeks' gestation with severe hypertensive disorders) were other key sources of evidence (Churchill et al 2013; Broekhuijsen et al 2015a; Vigil-De Gracia et al 2013; Koopmans et al 2009a; Sibai 2011). Additional identified sources were a systematic review that included observational studies (39 cohorts, 4,650 women at <34 weeks' gestation) (Magee et al 2009), studies looking at outcomes beyond 39 weeks' gestation and cost analysis (Lai et al 2016; Yuce et al 2015) and a study specifically addressing chronic hypertension and timing (Hutcheon et al 2011).

13.1 Gestational hypertension and pre-eclampsia without severe features

34+0 to 36+6 weeks' gestation

Expectant care has few differences in its risks or benefits to the woman, 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 (Sibai 2011). Considering the risk-benefit balance between the two management plans, expert opinion favours continued monitoring and birth after 37 weeks' gestation unless fetal indications or severe maternal features occur (Sibai 2011).

A meta-analysis of three RCTs (n=1773) (Chatzakis et al 2021) reported that for women with non-severe pre-eclampsia between 34+0 and 36+6 weeks' gestation, immediate birth decreased the risk of adverse maternal outcomes (composite adverse maternal outcome not defined beyond any of the potential pre-eclampsia-related complications ranging from severe hypertension to maternal death) by 14% but increased the risk of NICU admissions by 23%, compared with expectant management. No significant differences were reported for HELLP, eclampsia or severe pre-eclampsia when pregnancy was prolonged for an average of seven days.

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' gestation (Valent et al 2015).

37-39 weeks' gestation

A retrospective cohort study, looking at 683 singleton pregnancies complicated by hypertension 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% compared to 2.6%, $p = 0.04$) and a non-statistically significant increase in composite adverse maternal outcomes (0% compared to 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% compared to 10.3%, $p = 0.001$). This study suggests birth between 37 and 39 weeks' gestation offers the best maternal and neonatal outcomes for this group (Harper et al 2016). One population study specifically looking at chronic hypertension also suggested timing of 38–39 weeks' gestation as optimal, weighing maternal and fetal outcomes. However, the authors suggested post-term duration outcomes for this group needed larger RCT studies (Hutcheon et al 2011).

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 HDP was associated with a reduced risk of severe hypertension or HELLP syndrome (Koopmans et al 2009a). The composite adverse maternal outcome in the HYPITAT trial was significantly less frequent in womem who were randomised for induction of labour compared with women who were monitored expectantly (31% compared to 44%, RR 0.71, 95% CI 0.59–0.86 p < 0·0001). 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 (Koopmans et al 2009a; Broekhuijsen et al 2015b). 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%), FGR (10–12%) and fetal death (0.2–0.5%) (Sibai 2011). 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). Broekhuijsen et al (2015a) concluded that routine immediate birth did not seem justified.

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 and cost effectiveness is at the time of pre-eclampsia diagnosis at 36 weeks (Lai et al 2016).

Beyond 39 weeks' gestation

A maternal and fetal outcomes study compared 126 women who had gestational hypertension after 24 weeks' gestation but no other co-morbidities and 564 women with uncomplicated pregnancies (Yuce et al 2015). This study 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 $38+^{6}$ weeks' gestation (Apgar at 1 minute, p = 0.244; Apgar at 5 minutes, p= 0.527) but significantly worse at 39–41 weeks' gestation (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.

Another study included 683 women with hypertension at 36 weeks' gestation (Harper et al 2016). 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' gestation 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).

13.2 Severe pre-eclampsia and HELLP

Overall, the Cochrane systematic review (four trials, 425 women, 24–34 weeks' gestation with severe pre-eclampsia) and the MEXPRE Latin study (267 women, 28–33 weeks' gestation with severe hypertensive disorders) demonstrate that the evidence is insufficient to draw reliable conclusions about the comparative effects on most adverse outcomes for the woman (Churchill et al 2013; Vigil-De Gracia et al 2013).

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) (Churchill et al 2013). 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). 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 (Churchill et al 2013). 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) (Broekhuijsen et al 2015b; Sibai 2011). Babies of women in the interventionist group in the Cochrane review, however, were less likely to be SGA, which was also a finding of the MEXPRE Latin study (Vigil-De Gracia et al 2013) (RR 0.30; 95% CI 0.14–0.65).

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 (Magee et al 2009) 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' gestation with severe HDP) demonstrated that pregnancy was prolonged by 2.2 days for the interventionist group compared with 10.3 days for the expectant management group (Vigil-De Gracia 2013).

When pre-eclampsia occurs at a pre- or peri-viable gestation (under 24 weeks' 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% (Belghiti et al 2011; Budden et al 2006; Gaugler-Senden et al 2006; Sibai 2013;).

This evidence therefore suggests that an expectant approach to managing pregnant 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 pregnant woman/person.

The evidence is of very low quality, mainly from the HYPITAT study (women >36 weeks' gestation without severe features) and a review of observational studies among women with severe pre-eclampsia at less than 34 weeks' gestation (Koopmans et al 2009a; Magee et al 2009). 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 medicines (21%), antihypertensive medicines (16%), gestation past 41 weeks, (14%), rupture of membranes for more than 48 hours (5%), HELLP (4%) and severe proteinuria (2%) (Koopmans et al 2009a). 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 (Magee et al 2009). A systematic review also showed that corticosteroids do not improve mortality outcomes for HELLP (RR 0.95, 95% CI 0.28–3.21) (Woudstra et al 2010). 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) (Magee et al 2009). 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 pregnant woman/person before birth.

13.3 Indications for birth

Evidence suggests that the maternal indications for birth are: severe hypertension (refractory to treatment), HELLP, eclampsia, preterm labour or rupture of membranes, and vaginal bleeding (Sibai 2011; Sibai and Barton 2007). Fetal indications include: growth restriction/oligohydramnios, variable or late decelerations, absent or reverse umbilical artery diastolic flow, biophysical profile <6 (Sibai 2011) or issues with short-term variability on CTG (Lees et al 2015). These indications depend on the gestational age. Expert opinions from recent guidelines on managing HDP are consistent with this evidence on indications (Lowe et al 2015; Magee et al 2014; ACOG 2013).

Small for gestational age

Several studies have looked at determining the best gestational age for birth when the pregnancy is complicated by a HDP 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 (Aoki et al 2014; Belghiti et al 2011; Shear et al 2005).

13.4 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 pregnant women are at risk of preterm birth (Roberts et al 2006). Offer repeat doses of steroids if the risk of preterm birth is ongoing (Antenatal Corticosteroid Clinical Practice Guidelines Panel 2015). 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), ecrotizing 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) (Roberts et al 2006). 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** on antenatal corticosteroids suggests that steroids have good effect for preterm birth when gestational age is 34+6 weeks' gestation 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' gestation) (Antenatal Magnesium Sulphate for Neuroprotection Guideline Development Panel 2010).

Another Cochrane review of five trials (6,145 babies) demonstrated that giving women who are 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 reduced substantial gross motor dysfunction (RR 0.61, 95% CI 0.44–0.85) (Doyle et al 2009). The evidence from this review showed that the number of women needed to be treated for one baby to avoid cerebral palsy was (95% CI 43–155) (Moses et al 2015). 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).

14 Anaesthetic considerations

Anaesthesia – recommendations

Consider neuraxial methods of analgesia (that is, spinal, epidural and combined spinal and epidural anaesthesia, CSE) in labour, even for pregnant women/people with lower platelet counts. Do not recommend neuraxial methods when the platelet count is <80 × /L.

Strong recommendation; low-quality evidence

Do not recommend fluid preloading 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

If general anaesthesia (GA) is necessary, rapid sequence induction is the preferred technique. Aggressively prevent the hypertensive response to intubation.

Strong recommendation; low-quality evidence

Recommend propofol as an induction agent for GA.

Weak recommendation; very-low-quality evidence

Do not recommend central venous pressure monitoring.

Strong recommendation; very low-quality evidence

Do not recommend pulmonary artery catheterization.

Strong recommendation; very low-quality evidence

Consider a peripheral arterial line for monitoring BP.

Strong recommendation; very low-quality evidence

Continue magnesium sulphate during caesarean section.

Strong recommendation; low-quality evidence

Recommend fluid restriction to reduce the risk of fluid overload in the intrapartum and postpartum periods. Usually limit total fluids to 80–85 mL/hour for severe pre-eclampsia.

Strong recommendation; low-quality evidence

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

Good practice recommendation

A good working epidural in labour for a pregnant woman/person with a severe HDP may be useful to help reduce the hypertensive response to labour pain and 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/person's choice before opting for an epidural.

Good practice recommendation

Epidural analgesia lowers BP and may be a useful adjunct in treating a woman in labour 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 (GA) (Wallace et al 1995). Clinical practice recommendations stress that, with each method, it is necessary to specifically consider the risk-benefit balance and particular contraindications (Leffert 2015; Leone and Einav 2015; Dyer et al 2007).

14.1 General anaesthesia versus neuraxial techniques

Neuraxial anaesthesia is the preferred technique for pregnant women, including those with HDP (Cook et al 2009). Part of this support comes from the findings from some observational studies that maternal risk increases with GA (Okafor and Okezie 2005; Pant et al 2014), 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. However, epidural anaesthesia was associated with higher 1-minute Apgar scores (Moodley et al 2001). Another study that compared general with spinal anaesthesia demonstrated better haemodynamic stability with spinal anaesthesia during caesarean section in women with severe pre-eclampsia (Kinzhalova et al 2013). 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 (Wallace et al 1995). Specific indications for GA for caesarean section include coagulopathy and pulmonary oedema (Wallace et al 1995).

The major disadvantages of GA in pre-eclamptic women are the hypertensive response to intubation and the presence of laryngeal oedema, which contributes to an increased rate of difficult and failed intubation in obstetrics (Wallace et al 1995). The findings from an observational study (of 38 women) showed that, during GA, an additional intravenous bolus of magnesium sulphate 40 mg/kg was effective in obtunding the response to tracheal intubation (Ashton et al 1991). 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 GA when the magnesium bolus

was used in conjunction with remifentanil at 1.34 µg/kg (Yoo et al 2013). In women with severe pre-eclampsia, consider placing an arterial line before induction.

14.2 Providing general anaesthesia

The traditional technique for induction of GA in pregnant women/people 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 is widely accepted 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 pregnant woman/person. Users should therefore anticipate such a response and treat it in advance (Eldridge and Jaffer 2013). A bolus of remifentanil (1–1.5 µg/kg) is effective in obtunding the sympathetic response to laryngoscopy and has a very short duration of action in the newborn (Yoo et al 2013). If opioids are used 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 (Murdoch et al 2013). Other medicines, 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 (Davison and Cockerham 2016; Peer and Bhatia 2016).

Pregnant women/people in general are more difficult to intubate than their non-pregnant counterparts. Pregnant women/people with pre-eclampsia may have airway oedema, which makes intubating them even more difficult than other pregnant women/people. A strategy for GA should include a backup plan for airway management if a failed intubation occurs (Cook et al 2011).

GA for caesarean section is associated with an increased risk of awareness (Pandit et al 2013), so consider the depth of anaesthesia monitoring required. 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.

14.3 Magnesium sulphate

The evidence also shows that magnesium sulphate infusion is safe in the setting of regional anaesthesia (haemodynamic stability and coagulation) and GA (control of intubation response) (Dyer et al 2007). 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 (Dube and Granry 2003).

14.4 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 ($p < 0.001$) (Visalyaputra et al 2005). 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 similar in both groups (Visalyaputra et al 2005).

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 also less severe and required less ephedrine (Aya et al 2003; Aya et al 2005). Because of these effects, regional anaesthesia may provide additional control of hypertension if other methods are not proving effective in labour. Care should be taken to monitor for hypotension, particularly if the pregnant woman/person is on antihypertensive medicines.

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 (Dyer et al 2007; Henke et al 2013). Given the current evidence and clinical practice in some settings, this evidence statement 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 GA) if an emergency caesarean section is then required (Henke et al 2013).

14.5 Low platelet count

No reliable evidence is available on the lowest permissible platelet count for regional anaesthesia in pre-eclampsia (van Veen et al 2010). 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 (Sharma et al 1999). In addition, a study of 80 women demonstrated that 30 had an epidural anaesthetic placed when the platelet count was <100 × 10^9/L (range 69–98 × 10^9/L) and 22 had an epidural anaesthetic placed with a platelet count >100 × 10^9/L that subsequently decreased below 100 × 10^9/L. The study found no neurological complications (Beilin et al 1997).

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 (Leffert 2015; Dyer et al 2007; van Veen et al 2010). 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 GA are still greater (Goodier et al 2015).

14.6 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 (Henke et al 2013). Although preloading with intravenous fluids before traditional high-dose local anaesthetic blocks may have some benefits for the fetus and woman/person when the woman/person is healthy, no evidence specific to HDP 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 (Hofmeyr et al 2004). However, the studies were too small to draw conclusions to guide clinical practice and specifically the management of labour in hypertensive pregnant women/people.

14.7 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 (Young and Johanson 2001). Furthermore, evidence from a retrospective

study showed a high incidence of infection among women who received central venous catheters (Nuthalapaty et al 2009).

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 (Leffert 2015; Leone and Einav 2015). However, no randomised controlled clinical trials showing that pulmonary artery catheters are clinically more useful than echocardiographic techniques in hypertensive pregnancy were identified (Young and Johanson 2001). 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 (Dennis 2011).

15 Mode of birth

Mode of birth – recommendations

Recommend vaginal birth as the preferred mode of birth unless 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

Make the decision about mode of birth with the woman/person and the medical team (including obstetrics, neonatology and anaesthetics).

Weak recommendation; very low-quality evidence

Recommend vaginal birth with or without induction in pregnant women/people with pre-eclampsia but no other obstetric contraindications.

Weak recommendation; very low-quality evidence

Consider caesarean before 28 weeks' gestation because labour induction is less successful and maternal and fetal disease is likely to be more severe.

Weak recommendation; very low-quality evidence

Actively managing the third stage of labour.

Strong recommendation; very low-quality evidence

Avoid ergometrine and Syntometrine® as an uterotonic in pregnant women/people with HDP except when massive obstetric haemorrhage occurs.

Weak recommendation; very low-quality evidence

After deciding and agreeing on the intervention to end the pregnancy, consider the mode of birth. The primary consideration is the urgency of the baby's birth for the woman/person's benefit.

15.1 Induction versus elective caesarean section

When assessing a woman/person with hypertension or pre-eclampsia for induction or caesarean section, base the decision on best evidence, the clinical picture, local guidelines and the woman/person's preferences. The current evidence focuses mainly on severe pre-eclampsia. It comes from the outcomes of the HYPITAT (Koopmans et al 2009a) and HYPITAT-II (Broekhuijsen et al 2015b) 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 the woman or baby if it was not absolutely necessary (Coppage and Polzin 2002). 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 woman 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-eclampsia (Coppage and Polzin 2002). 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 (Amorim et al 2015). The 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).

Pacher et al (2014) 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, $p = 0.001$).

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 pregnant women with HDP (RR 0.75, 95% CI 0.55–1.04 and RR 0.94, 95% CI 0.75–1.16,

respectively) compared with expectant management (Koopmans et al 2009a; Broekhuijsen et al 2015b). 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). HYPITAT found no significant difference in this area (Broekhuijsen et al 2015b).

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 (Alexander 1999; Chibber 2002). 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 5 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 (Alexander 1999; Chibber 2002).

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). The study showed that induction of labour does not affect the clinical and biochemical cardiovascular profile at 2.5 years postpartum (Hermes et al 2013).

15.2 Induction outcomes

Alanis et al (2008) 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. 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. 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).

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 (Xenakis 1997). 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 (Xenakis et al 1997). Kim et al's retrospective cohort study of 3,505 women Kim et al 2010) 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 pregnant 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 (Broekhuijsen et al 2015a). However, because the data suggests that neonatal outcomes are better in emergency caesarean sections than elective ones (Chibber 2002; Pacher et al 2014), pregnant women with pre-eclampsia and no contraindications should be encouraged to consider induction as an option.

15.3 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 (Nassar et al 1998). The 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 5 minutes or postpartum endometritis (Nasser et al 1998).

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 (van der Tuuk et al 2015). Of the 756 pregnant 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 (van der Tuuk et al 2015).

Researchers have looked at various other models of influence on the success rate of induction, including one study that examined obesity as a predictive factor (Robinson et al

2010). 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, with even small increases (5 units) in BMI associated with a 16% increase in the odds of caesarean birth.

Another small prospective study in Japan (Shibata et al 2016) 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 BP); uncontrollable rises in BP and ineffective labour induction (measured against a set definition of progress).

15.4 Methods of induction

Methods of labour induction in clinical practice include administering pharmaceutical agents (such as oxytocin, prostaglandin E2 or misoprostol) and mechanical methods. This section presents evidence of 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 of 5 or less), helped reduce the caesarean section rate (compared with the rate for those with a favourable cervix) (Tajik et al 2012). A Cochrane review used two studies (n = 234) to compare Bishop score with transvaginal ultrasound (TVUS) to assess pre-induction cervical ripening in pregnant women admitted for induction. 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) (Ezebialu et al 2015).

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 (Nuutila and Kajanoja 1995). 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 (Nuutila and Kajnoja 1995).

15.5 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 (Eskild and Vatten 2009). 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 BP ($p < 0.01$). 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) (Eskild and Vatten 2009).

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) (von Schmidt auf Altenstadt et al 2013). 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/person. 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-eclampsia (Reyes and Gonzalez 2011).

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 (Dua 1994; Ng et al 2018). However, it may be of benefit if severe haemorrhage occurs.

16 Long-term risks

Long-term risks – recommendations

Give pregnant women/people with a history of HDP information on long-term risks of pre-eclampsia, including cardiovascular disease, and the importance of following a healthy lifestyle. (See Table 2 below for a list of these risks.)

Strong recommendation; very low-quality evidence.

Give pregnant women/people with a history of pre-eclampsia information on risks linked with subsequent pregnancies. Give them the opportunity to discuss contraceptive options.

Weak recommendation; very low-quality evidence

GP follow-up: Assess pregnant women/people with a history of pre-eclampsia for BP, lipids, HbA1c, thyroid function and BMI.

Weak recommendation; very low-quality evidence

Hospital to send a comprehensive discharge summary to the pregnant woman/person and their LMC and GP, including postpartum plan of care, monitoring and specific advice on antihypertensive medication. This is particularly important for arranging long-term, ongoing follow-up.

Good practice recommendation

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

Good practice recommendation

Within days of a pre-eclamptic pregnancy – 16 days on average – BP 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 (Irgens et al 2001; van Baaren et al 2014).

Despite their recovery to a normal BP, evidence indicates that many women who have had pre-eclampsia will develop long-term complications (Williams 2011). 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 (Irgens et al 2001; Skjaerven et al 2012). Studies indicate that annual hypertension screening and treatment in primary health care for women who have experienced pre-eclampsia at any gestation could be cost effective in preventing future cardiovascular disease (van Baaren et al 2014; Drost et al 2015).

16.1 Future pregnancies

A woman who has had pre-eclampsia in their first pregnancy has a higher risk of gestational hypertension (RR 6.3, 95% CI 3.4–12) (Zhang et al 2001) 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) (Duckitt and Harrington 2005). Having gestational hypertension also increases the risk that a woman will experience it again (RR 3.4, 95% CI 2.0–5.8) (Zhang et al 2001) or pre-eclampsia (OR 7.57, 95% CI 2.31–24.78) (Brown et al 2007) in a subsequent pregnancy.

Health professionals can give women/people advice about reducing risk factors for future pregnancies, such as ways of lowering BMI. However, no studies have proven that this approach will reduce the incidence when women/people are already at high risk. Further, they may not be able to modify some risk factors, for example, age. A woman may wish to consider their contraceptive options in such situations (Skurnik et al 2016).

16.2 Cardiovascular disease

Studies have reported that 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 HDP representing an earlier stage on the path to cardiovascular problems (Magee et al 2014).

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 (Brown et al 2013). The evidence from this review demonstrates that women with a history of pre-eclampsia are approximately two times more likely to develop CVD (OR 2.28, 95% CI 1.87–2.78) and cerebrovascular disease (OR 1.76, 95% CI 1.43–2.21) and three times more likely to develop hypertension (RR 3.13, 95% CI 2.51–3.89) that those with no such history (Brown et al 2013). These findings are consistent with the findings from earlier meta- analyses (Bellamy et al 2007; McDonald et al 2008; Skjaerven et al 2012). However, Brown et al (2013) found no evidence that the risk of CVD increases when pre-eclampsia is associated with preterm birth (RR 1.32, 95% CI 0.79–2.22).

Other studies show that women with gestational hypertension are at higher risk of later developing chronic hypertension (RR 3.39, 95% CI 0.82–13.9), CVD (RR 1.66, 95% CI 0.62–4.41) (Bellamy et al 2007) and cerebrovascular disease (RR 1.47; 95% CI 1.05 – 2.0) (Jónsdóttir et al 1995). Another study (Berks et al 2013) 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) 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 stroke are 1.89 (IQR 1.76–1.98) and 1.55 (IQR 1.40–1.71) respectively (Berks et al 2013).

16.3 Other diseases

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) (Bellamy et al 2007).

Thyroid disease

Two prospective population-based cohort studies, the Northern Finland Birth Cohorts 1966 and 1986 (Männistö et al 2013), followed women who had pre-eclampsia (n = 955) or normal BP (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.

Diabetes

Because pre-eclampsia is linked with a woman/person's BMI, 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 that the incidence of type 2 diabetes increases in women who have had a pregnancy complicated by pre-eclampsia (Williams 2011). 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 (Libby et al 2007). Another study from the USA 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 (Khan et al 2006).

Renal disease

Researchers believe that pre-eclampsia-triggered metabolic stress may cause vascular injury, thus contributing to the development of CVD and/or CKD in the future (Maruotti et al 2012).

In one study, pre-eclampsia during the first pregnancy was associated with a relative risk of end-stage renal disease of 4.7 (Vikse et al 2008). 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 greater (McDonald et al 2010).

Cognitive effects

Zeeman 2009) suggested that the pathophysiology of eclampsia represents an expression of posterior reversible encephalopathy syndrome characterised by lesions in the brain due to ischaemia and oedema affecting cognitive function in the short and long term. 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. Another study of 92 women (Aukes et al 2007) observed that formerly eclamptic women scored significantly higher on the Cognitive Failures Questionnaire than healthy parous control subjects, and women who experienced multiple eclamptic seizures reported more cognitive impairment than those who had experienced one seizure.

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 (Brussé et al 2008). In this study, the differences in levels of intellectual functioning, language tests, attention and concentration tests and executive functioning, depression and anxiety scores 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 ($p < 0.05$) subscales (Postma et al 2014).

Other long-term effects such as visual loss have been related to the cerebral ischaemia and lesions associated with HDP. However, 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 pre-eclampsia (Wiegman et al 2012).

16.4 Effects on the baby

Berks et al (2013), conducting a systematic review of 18 cohort and case-control studies (n = 45,249 individuals aged 4–30 years) to look at the effects on the children of women who experienced pre-eclampsia, found they had an increased risk of CVD. 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 dBP during childhood and young adulthood. 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 (Davis et al 2012). 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 (Herrera-Garcia and Contag 2014).

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 (Kronenberg et al 2006). 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 BP (Whitehouse et al 2012). 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.

16.5 Other factors – clinical use and pregnant women's/people'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 pregnant women/people, health professionals need to customise the evidence they present to suit each individual woman/person'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 parenthood, so health professionals must allow them time to become fully engaged with the information (Brown et a; 2013).

- No studies have established whether postnatal lifestyle changes will reduce long-term effects for women/people who have experienced HDP. More evidence is required in this area.

Table 2: Risk of developing long-term conditions for pregnant women/people who have ad gestational hypertension or pre-eclampsia

Future risk	HDP (index pregnancy)	
	Gestational hypertension*	Pre-eclampsia
	Relative risk (95%CI)	
Gestational hypertension in future pregnancy	3.4 (2.0–5.8) (Zhang et al 2001)	6.3 (3.4–12.0) (Zhang et al 2001)
Pre-eclampsia in future pregnancy	7.6 (2.3–24.8) (Brown et al 2007)**	7.2 (5.9–8.8) (Duckitt and Harrington 2005)
Chronic hypertension	3.4 (0.8–13.9) (Bellamy et al 2007)	3.1 (2.5–3.9) (Brown et al 2013)
Cardiovascular disease	1.7 (0.6–4.4) (Bellamy et al 2007)	2.3 (1.9–2.8) (Brown et al 2013)
Cerebrovascular disease	1.5(1.1–2.0) (Jónsdóttir et al 1995)	1.8(1.4–2.2) (Bellamy et al 2007)
Venous thromboembolism	–	1.8 (1.4–2.3) (Bellamy et al 2007)
End-stage kidney disease	–	4.3 (3.3–5.6) (Vikse et al 2008)

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

** Odds ratio

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.
Antenatal	Occurring before birth; concerned with the care and treatment of the unborn child and pregnant woman/person.
Body mass index (BMI)	The body's weight in kilograms divided by the square of the woman's/person's height in metres. This 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 Cochrane (formerly the Cochrane Collaboration), an international and independent not-for-profit organisation formed to provide accurate information about worldwide health care. Available electronically as part of the Cochrane Library.
Confidence interval (CI)	A range of values for a population outcome estimated from a study. The CI will depend on the number of study recruits and the variation in the outcome data. A 95% CI means that if the study were 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 Cis, 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 medicine.
Eclampsia	Seizures (convulsions) in a pregnant woman/person related to HDP.

Evidence statement	A table 98ummarizing the results of a collection of studies, which together represent the evidence supporting a recommendation or series of recommendations in a guideline.
Expectant management	Continuation of a pregnancy beyond 48 hours while monitoring the woman/person and the fetus, rather than applying an intervention, such as caesarian section.
Fetal	Of or relating to a fetus or to the period of the development of the fetus.
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.
Hypertension	High blood pressure.
Intrapartum	Relating to the period of labour and birth.
Multidisciplinary team (MDT)	A team that may include, as relevant to the clinical circumstances, an obstetrician, midwives, an obstetric physician, an anaesthetist and/or a neonatologist/paediatrician experienced in the care of women/people 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 to be treated with 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 these evidence statements, the obstetric team is a specialist team that will include an obstetric specialist and registrar and may also include an 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 (for example, a disease prevalent in less than 10% of the population), the OR will be approximately the same as the RR. However, it is defined as the ratio of the relative odds of the outcome occurring in one group compared with another group and is used when the absolute risk (risk in the 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 medicine.
Postnatal	Occurring after birth; concerned with the care and treatment of the baby and woman/person after birth.
Postpartum	The period of time after birth.
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, for example, large studies can detect small differences.
Randomised controlled trial (RCT)	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	*Guidelines for Consultation with Obstetric and Related Medical Services (Referral Guidelines)* (Ministry of Health 2012)
Regimen	A pattern of treatment such as dose or frequency of a medicine.
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. An RR of one indicates no difference between comparison groups. For undesirable outcomes, an RR 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.
Sample size	The number of units (women, 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 tenth birthweight centile or a fetus with an estimated fetal weight on a customised growth chart less than the tenth customised centile for gestation.
Spot urine	The sampling of a single, untimed urine specimen, voided spontaneously by the patient.
Stillbirth	Death in a fetus that weighs 400 g or more or is 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.

Abbreviations used in these evidence statements

ABPM	Ambulatory blood pressure monitoring
ACE	Angiotensin converting enzyme
AFV	Amniotic fluid volume
ALT	Alanine transaminase
AOR	Adjusted odds ratio
ART	Assisted reproductive technology
AST	Aspartate transaminase
AUC ROC	Area under the receiving operating characteristics curve
BMI	Body mass index
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
FGR	Fetal growth restriction
GA	General anaesthesia
GP	General practitioner (family doctor)
hCG	Human chorionic gonadotropin
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
LMC	Lead maternity carer

MAP	Mean Arterial Pressure
MPV	Mean platelet volume
NICE	National Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NNT	Number needed to treat
NNTH	Number needed to harm
NSAIDs	Nonsteroidal anti-inflammatory medicines
OR	Odds ratio
PAPP-A	Pregnancy associated plasma protein A
PGE2	Prostaglandin E2
PIERS model	Pre-eclampsia integrated estimate of risk model
PIGF	Placental growth factor
PP-13	Placenta protein-13
PPSMC	Pre-eclampsia prenatal symptom-monitoring scale
PPV	Positive predictive value
PTSD	Post-traumatic stress disorder
RCT	Randomised controlled trial
sBP	Systolic blood pressure
SF	symphysio-fundal
s-Flt-1	soluble fms-like tyrosine kinase 1
SGA	Small for gestational age
TVUS	Transvaginal ultrasound
UtA	Uterine artery
UADV	Uterine artery Doppler velocimetry
V TE	Venous thromboembolism
WHO	World Health Organization

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