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# Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health

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## Review

# Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy



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## ABSTRACT

**Objective:** This guideline summarizes the quality of the evidence to date and provides a reasonable approach to the diagnosis, evaluation and treatment of the hypertensive disorders of pregnancy (HDP).

**Evidence:** The literature reviewed included the previous Society of Obstetricians and Gynaecologists of Canada (SOGC) HDP guidelines from 2008 and their reference lists, and an update from 2006. Medline, Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Registry of Controlled Trials (CCRCT) and Database of Abstracts and Reviews of Effects (DARE) were searched for literature published between January 2006 and March 2012. Articles were restricted to those published in French or English. Recommendations were evaluated using the criteria of the Canadian Task Force on Preventive Health Care and GRADE.

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**Abbreviations:** ABPM, ambulatory blood pressure monitoring; ACE, angiotensin converting enzyme; ACR, albumin to creatinine ratio; ALT, alanine transaminase; aPTT, activated partial thromboplastin time; ARB, angiotensin receptor blocker; AST, aspartate transaminase; BMI, body mass index; Booking, first antenatal visit, usually early in pregnancy; BP, blood pressure; CHEP, Canadian Hypertension Education Program; CHS, Canadian Hypertension Society; CI, confidence interval; CVP, central venous pressure; DASH, Dietary Approaches to Stop Hypertension; FHR, fetal heart rate; HELLIP, haemolysis, elevated liver enzymes, low platelets; HBPM, home blood pressure monitoring; hCG, human chorionic gonadotropin; HDP, hypertensive disorders of pregnancy; IM, intramuscular; IUGR, intrauterine growth restriction; IV, intravenous; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; MgSO<sub>4</sub>, magnesium sulfate; mmHg, millimeters of mercury; NICE, National Institute for Health and Clinical Excellence; NICU, neonatal intensive care unit; NNT, number needed to treat; NSAID, non-steroidal anti-inflammatory drug; po, per os; RCT, randomized controlled trial; RR, relative risk; SGA, small for gestational age; SOGC, Society of Obstetricians and Gynaecologists of Canada; UTI, urinary tract infection; WHO, World Health Organization.

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## Introduction

The hypertensive disorders of pregnancy (HDP) remain leading causes of maternal and perinatal morbidity and mortality [1,2]. This guideline summarizes the quality of the relevant existing evidence and provides a reasonable approach to the diagnosis, evaluation, and treatment of the HDP.

Our **purpose** is to support evidence-based maternity care of women who: are planning pregnancy and are at risk of a HDP, have a HDP in the current pregnancy, or are postpartum and had a HDP. When necessary, we have provided expert opinion about reasonable clinical care. The information should not be taken to dictate an exclusive course of care, and is amenable to well-documented local amendments. Our **health intent and aim** is, for pregnancies complicated by a HDP, to improve short- and long-term maternal, perinatal, and paediatric outcomes, and related cost-effectiveness of interventions. The **expected benefit** of using this guideline is improved outcomes for mother, baby, and child, through evidence-advised practice. The **target users** are multidisciplinary maternity care providers from primary to tertiary levels of health care.

The **questions** that this guideline seeks to address are:

- How, and in what setting, should blood pressure (BP) be measured in pregnancy and what is an abnormal BP?
- How should proteinuria be measured in pregnancy? What constitutes significant proteinuria? Is heavy proteinuria an indication for delivery?
- How should the HDP be diagnosed and classified? What constitutes severe preeclampsia?
- What is the prognosis of pregnancies complicated by pre-existing hypertension, gestational hypertension, or preeclampsia?
- How can preeclampsia and its complications be predicted and/or prevented by lifestyle changes, medication and/or care of a specific type or in a specific location?
- How should women with a HDP be managed with regard to: initial investigations; dietary and lifestyle change; place of care; antihypertensive therapy; aspects of care specific to women with preeclampsia (such as magnesium sulfate); mode and timing of delivery; intrapartum care (including BP monitoring and analgesia/anaesthesia); and postpartum monitoring, treatment, and counselling regarding the impact of a HDP on both future pregnancy outcomes and long-term maternal and paediatric outcomes?
- What is the perspective of the patient with regard to diagnosis and evaluation?
- How can this guideline be implemented into clinical practice?

## Methods

The guideline was developed by a methodologist and maternity care providers (from obstetrics, internal medicine, anaesthesia, and paediatrics) knowledgeable about the HDP and guideline development.

The literature reviewed included the previous (2008) SOGC HDP guideline and its references [3] covering articles until July 2006, as well as updated literature from January

2006 until March 2012, using a search strategy similar to that for the 2008 guideline (and available upon request); a notable addition was exploration of the perspective and interests of patients with a HDP [4]. Literature reviews were conducted by librarians of the College of Physicians and Surgeons of British Columbia and University of British Columbia, restricting articles to those published in English and French.

We prioritized randomized controlled trials (RCTs) and systematic reviews (if available) for therapies and evaluated substantive clinical outcomes for mothers (death; serious morbidity, including eclampsia, HELLP syndrome, and other major end-organ complications; severe hypertension; placental abruption; preterm delivery; Caesarean delivery; maternal adverse effects of drug therapies or other interventions; and long-term health) and babies (perinatal death, stillbirth, and neonatal death; small for gestational age infants; NICU care; serious neonatal morbidity, and long-term paediatric health and neurodevelopment).

All authors graded the quality of the evidence and their recommendations, using the Canadian Task Force on Preventive Health Care (Appendix Table A1) [5] and GRADE (Level of evidence/Strength of recommendation, Appendix Table A2) [6].

This document was reviewed by the Executive and Council of the SOGC, and the approved recommendations published on the SOGC website as an Executive Summary ([www.sogc.com](http://www.sogc.com)).

## Chapter 1: Diagnosis and classification of the HDPs

### Measurement of BP

#### Recommendations

1. BP should be measured with the woman in the sitting position with the arm at the level of the heart (II-2A; Low/Strong).
2. An appropriately sized cuff (i.e., length of 1.5 times the circumference of the arm) should be used (II-2A; Low/Strong).
3. Korotkoff phase V should be used to designate diastolic BP (I-A; Moderate/Strong).
4. If BP is consistently higher in one arm, the arm with the higher values should be used for all BP measurements (III-B; Very low/Weak).
5. BP can be measured using a mercury sphygmomanometer, calibrated aneroid device, or an automated BP machine that has been validated for use in preeclampsia (II-2A; Low/Strong).
6. Automated BP machines that have not been validated for use in preeclampsia may under- or over-estimate BP in those women and comparison of readings using mercury sphygmomanometry or a calibrated aneroid device is recommended (II-2A; Low/Strong).
7. In the office setting, when BP elevation is non-severe and preeclampsia is not suspected, either ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) is useful to confirm persistently elevated BP (II-2C; Very low/Weak).

8. When HBPM is used, maternity care providers should ensure that patients have adequate training in measuring their BP and interpreting the readings taken (III-C; Very low/Strong).
9. The accuracy of all BP measurement devices used in hospitals or offices should be checked regularly against a calibrated device (II-3C; Very low/Strong).
10. The accuracy of all automated devices used for HBPM should be checked regularly against a calibrated device (III-C; Very low/Strong).

#### Comments

BP measurement in pregnancy should use non-pregnancy standardized technique [7,8]. BP may be measured by ambulatory BP monitoring (ABPM) or home BP monitoring (HBPM) [9], using auscultatory or automated methods [10]. Most clinics and hospitals use aneroid or automated devices.

ABPM comprehensively measures BP, either in a community setting (serially over 24 h using an automated device) or by serial BP measurements in an obstetrical day unit.

HBPM is done by the woman using an automated device, with duplicate measurements taken at least twice daily over several days [7,11]. When HBPM values are normal but office values elevated, ABPM or repeated HBPM are recommended [7].

While pregnant women and practitioners prefer HBPM to ABPM [12], pregnancy data are insufficient to guide choice. Patients require education about monitoring procedures and interpretation of BP values, especially the threshold for alerting maternity care providers.

A comprehensive list of approved devices for HBPM can be found at <http://www.dableducational.org>, <http://www.bhsoc.org/default.stm>, and <http://www.hypertension.ca/devices-endorsed-by-hypertension-canada-dp1>. Women should use pregnancy- and preeclampsia-validated devices; if unavailable, clinicians should compare contemporaneous HBPM and office readings (see 'Diagnosis of Hypertension').

#### Diagnosis of hypertension

##### Recommendations

1. The diagnosis of hypertension should be based on office or in-hospital BP measurements (II-B; Low/Strong).
2. Hypertension in pregnancy should be defined as an office (or hospital) sBP  $\geq 140$  mmHg and/or dBP  $\geq 90$  mmHg, based on the average of *at least* two measurements, taken at least 15 min apart, using the same arm (II-2B; Low/Weak for sBP and Low/Strong for dBP).
3. 'Resistant' hypertension should be defined as the need for three antihypertensive medications for BP control at  $\geq 20$  weeks' gestation (IIIC; Low/Weak).
4. A 'transient' hypertensive effect should be defined as office sBP  $\geq 140$  mmHg or a dBP  $\geq 90$  mmHg which is not confirmed after rest, or on repeat measurement on the same or on subsequent visits (II-2B; Very low/Weak).
5. A 'white coat' hypertensive effect refers to BP that is elevated in the office (i.e., sBP  $\geq 140$  mmHg or dBP  $\geq$

- 90 mmHg) but ABPM or HBPM sBP is  $<135$  mmHg and dBP is  $<85$  mmHg (II-2B; Very low/Strong).
6. A 'masked' hypertensive effect refers to BP that is normal in the office (i.e., sBP  $<140$  mmHg and dBP  $<90$  mmHg) but elevated by ABPM or HBPM (i.e., sBP  $\geq 135$  mmHg or dBP  $\geq 85$  mmHg) (II-2B; Very low/Weak).
7. Severe hypertension should be defined, in any setting, as a sBP of  $\geq 160$  mmHg or a dBP of  $\geq 110$  mmHg based on the average of *at least* two measurements, taken at least 15 min apart, using the same arm (II-2B; Low/Strong).

#### Comments

Hypertension in pregnancy is defined by office (or in-hospital) sBP  $\geq 140$  mmHg and/or dBP  $\geq 90$  mmHg [7,9,13]. We have recommended use of sBP and dBP to both raise the profile of sBP (given inadequate treatment of severe systolic hypertension) and for consistency with other international documents. We recommend repeat (office or community) BP measurement to exclude transient BP elevation (see below).

Non-severely elevated BP should be confirmed by repeat measurement, at least 15 min apart at that visit. BP should be measured three times; the first value is disregarded, and the average of the second and third taken as the BP value for the visit [7]. Up to 70% of women with an office BP of  $\geq 140/90$  mmHg have normal BP on subsequent measurements on the same visit, or by ABPM or HBPM [14–18]. The timing of reassessment should consider that elevated office BP may reflect a situational BP rise, 'white coat' effect, or early preeclampsia [19,20].

Office BP measurements may normalize on repeat measurement, called 'transient hypertension'. When BP is elevated in the office but normal in the community (i.e., daytime ABPM or average HBPM is  $<135/85$  mmHg), this is called 'white coat' effect [21–23]. When BP is normal in the office but elevated in the community, this is called 'masked hypertension' [24]. The difference in what is considered a normal BP in the office ( $<140/90$  mmHg) vs. in the community ( $<135/85$  mmHg) is important to note for outpatient BP monitoring.

Severe hypertension as sBP  $\geq 160$  mmHg (instead of 170 mmHg) reflects stroke risk [2,25].

#### Measurement of proteinuria

##### Recommendations

1. All pregnant women should be assessed for proteinuria (II-2B; Low/Weak).
2. Urinary dipstick testing (by visual or automated testing) may be used for screening for proteinuria when the suspicion of preeclampsia is low (II-2B; Low/Weak).
3. Significant proteinuria should be defined as  $\geq 0.3$  g/d in a complete 24-h urine collection or  $\geq 30$  mg/mmol urinary creatinine in a spot (random) urine sample (II-2B; Moderate/Strong).
4. Significant proteinuria should be suspected when urinary dipstick proteinuria is  $\geq 1+$  (II-2A; Moderate/Strong).

5. More definitive testing for proteinuria (by urinary protein:creatinine ratio or 24-h urine collection) is encouraged when there is a suspicion of preeclampsia, including:  $\geq 1+$  dipstick proteinuria, in the setting of hypertension with rising BP, or when BP is normal but women have symptoms or signs suggestive of preeclampsia (II-2A; Moderate/Strong).
6. Proteinuria testing does not need to be repeated once the significant proteinuria of preeclampsia has been confirmed (II-2A; Moderate/Strong).
7. There is insufficient information to make a recommendation about the accuracy of the urinary albumin:creatinine ratio (II-2 L; Low/Strong).

#### Comments

All pregnant women should be assessed for proteinuria [26] in early pregnancy to detect pre-existing renal disease, and at  $\geq 20$  weeks to screen for preeclampsia in those at increased risk. Benign and transient causes should be considered (e.g., exercise-induced, orthostatic, or secondary [e.g., UTI] proteinuria).

Proteinuria diagnosis can be performed on random samples [by urinary dipstick, protein:creatinine ratio (PrCr), or albumin:creatinine ratio (ACR)] or timed urine collections (usually 24-h). Quantification of urinary protein by 24-h urine collection is often inaccurate [27], and has been replaced by spot urine samples outside pregnancy [28].

A dipstick value of 1+ proteinuria has low sensitivity (55%, 95% CI 37–72%); a negative or 'trace' result should not exclude further investigation if preeclampsia is suspected [29]. Urinary dipstick testing has reasonable specificity (84%, 95% CI 57–95%) for significant proteinuria [29]; a  $\geq 1+$  result should prompt additional investigations (even with low suspicion of preeclampsia) and a  $\geq 2+$  result strongly suggests 0.3 g/d. Whether automated dipstick testing exhibits similar diagnostic test properties is not yet clear [30,31].

A PrCr of  $\geq 30$  g/mol represents significant proteinuria in singleton pregnancy [32]; a threshold up to 40 g/mol may be more appropriate in multiple pregnancy [33,34]. Outside pregnancy, early morning urine samples should be tested as the most concentrated of the day [34–37].

ACR has published cut-offs of 2–8 mg/mmol for detection of 0.3 g/d proteinuria; it is not currently recommended [30,38–42].

We suggest screening with urinary dipstick at each antenatal visit. Proteinuria should be quantified (by PrCr or 24 h urine collection) if preeclampsia is suspected (see 'Investigations for classification').

#### Classification of HDP

##### Recommendations

1. Hypertensive disorders of pregnancy should be classified as pre-existing hypertension, gestational hypertension, preeclampsia, or 'other hypertensive effects' based on different diagnostic and therapeutic considerations. (II-2B; Low/Strong).

2. The presence or absence of preeclampsia must be ascertained, given its clear association with more adverse maternal and perinatal outcomes (II-2B; Low/Strong).
3. In women with pre-existing hypertension, preeclampsia should be defined as resistant hypertension, new or worsening proteinuria, one or more adverse conditions, or one or more severe complications (II-2B; Low/Strong).
4. In women with gestational hypertension, preeclampsia should be defined as new-onset proteinuria, one or more adverse conditions, or one or more severe complications (II-2B; Low/Strong).
5. Severe preeclampsia should be defined as preeclampsia complicated by one or more severe complications (II-2B; Low/Strong).
6. Severe preeclampsia, as defined in this guideline, warrants delivery (II-2B; Low/Strong).
7. The term PIH (pregnancy-induced hypertension) should be abandoned, as its meaning in clinical practice is unclear (III-D; Low/Strong).

#### Comments

The HDP are classified as pre-existing hypertension, gestational hypertension, or preeclampsia among whom 'other hypertensive effects' can also be observed (Table 1) (see *Diagnosis of Hypertension*). A final diagnosis of HDP type is made at 6 weeks postpartum.

Approximately 1% of pregnancies are complicated by pre-existing hypertension, 5–6% by gestational hypertension, and 1–2% by preeclampsia; [43]. Rates of all are anticipated to rise given older and more obese obstetric populations with more antecedent medical complications.

For pre-existing and gestational hypertension, there are two subgroups: (1) with comorbid conditions that mandate tighter BP control as outside pregnancy (to protect end-organ function) [7], and (2) with preeclampsia (given its substantial maternal and perinatal risks).

We added a new category of 'other hypertensive effects' to raise awareness that office BP that is not consistently elevated may still be associated with elevated risks compared with consistently normal BP.

*Pre-existing (chronic) hypertension.* This pre-dates pregnancy or appears before 20 weeks. Heightened risks of adverse outcomes include: superimposed pre-eclampsia (~20%) [44–57], half of which develops at term [46,47,52,54,58], preterm delivery (about 33%) [44–50,52–54,56,57], abruption (1.8%), IUGR (~15%) [44–52], stillbirth (0.1% by 36 weeks [equivalent to risk at 41 weeks in low risk pregnancies]), and NICU admission (up to 50%) [54–59].

*Gestational hypertension.* This appears at  $\geq 20$  weeks. By ABPM,  $\approx 30\%$  of women with hypertension at  $\geq 20$  weeks demonstrate white coat effect ( $\approx 70\%$  in third trimester) [60]. Associated risks depend on gestational age at presentation and progression to preeclampsia; gestational hypertension at  $< 34$  weeks is associated with a  $\sim 35\%$  risk of preeclampsia which takes an average of 5 weeks to develop [61–66].

**Table 1**  
Classification of the HDP.

	Comments
<b>Pre-existing (chronic) hypertension</b>	This is defined as hypertension that was present either pre-pregnancy or that develops at <20 <sup>0</sup> weeks gestation
• With comorbid condition(s)	Comorbid conditions (e.g., pre-gestational type I or II diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened cardiovascular risk
• With evidence of preeclampsia	This is also known as 'superimposed preeclampsia' and is defined by the development of one or more of the following at ≥ 20 weeks: <ul style="list-style-type: none"> <li>• Resistant hypertension, or</li> <li>• New or worsening proteinuria, or</li> <li>• One/more adverse condition(s)<sup>¥</sup> or</li> <li>• One/more severe complication(s)<sup>¥</sup></li> </ul> Severe preeclampsia is defined as preeclampsia with one or more severe complication(s)
<b>Gestational hypertension</b>	This is defined as hypertension that develops for the first time at ≥ 20 <sup>0</sup> weeks' gestation
• With comorbid condition(s)	Comorbid conditions (e.g., pregestational type I or II diabetes mellitus or kidney disease) warrant tighter BP control outside of pregnancy because of their association with heightened cardiovascular risk
• With evidence of preeclampsia	Evidence of preeclampsia may appear many weeks after the onset of gestational hypertension. Preeclampsia is defined by gestational hypertension and one or more of the following: <ul style="list-style-type: none"> <li>• New proteinuria, or</li> <li>• One/more adverse condition(s)<sup>¥</sup> or</li> <li>• One/more severe complication(s)<sup>¥</sup></li> </ul> Severe preeclampsia is defined as preeclampsia with one or more severe complication(s)
<b>Preeclampsia</b>	Preeclampsia may arise <i>de novo</i> . It is defined by gestational hypertension and one or more of the following: <ul style="list-style-type: none"> <li>• New proteinuria, or</li> <li>• One/more adverse condition(s)<sup>¥</sup> or</li> <li>• One/more severe complication(s)<sup>¥</sup></li> </ul> Severe preeclampsia is defined as preeclampsia with one or more severe complications <sup>¥</sup>
<b>'Other hypertensive effects'</b> <sup>*</sup>	
Transient hypertensive effect	Elevated BP may be due to environmental stimuli or the pain of labour, for example
White coat hypertensive effect	BP that is elevated in the office (sBP ≥ 140 mmHg or dBP ≥ 90 mmHg) but is consistently normal outside of the office (<135/85 mmHg) by ABPM or HBPM
Masked hypertensive effect	BP that is consistently normal in the office (sBP < 140 mmHg or dBP < 90 mmHg) but is elevated outside of the office (≥ 135/85 mmHg) by ABPM or repeated HBPM

ABPM, ambulatory BP monitoring; BP, blood pressure; HBPM, home BP monitoring.

<sup>\*</sup> These may occur in women whose BP is elevated at <20<sup>0</sup> or ≥20<sup>0</sup> weeks who are suspected of having pre-existing or gestational hypertension/preeclampsia, respectively.

<sup>¥</sup> Please see Table 2 for definitions of adverse conditions and severe complications of preeclampsia.

**Preeclampsia.** This is the HDP associated with the greatest risks, particularly when it is severe or present at <34 weeks. The risk of SGA infants is primarily among women who present at <34 weeks, with macrosomia more common with term preeclampsia [67].

#### ○ The pathogenesis of preeclampsia

Preeclampsia results from a mismatch between utero-placental supply and fetal demands, leading to its systemic inflammatory maternal (and fetal) manifestations (Fig. 1) [68,69].

The most common maternal manifestations define preeclampsia clinically: hypertension and proteinuria. Other manifestations reflect end-organ dysfunction and are non-specific. Stroke [2,25], and pulmonary oedema are leading causes of maternal death in preeclampsia [25]. Jaundice is a late finding or may reflect another diagnosis (e.g., acute fatty liver of pregnancy). Eclamptic seizures are usually isolated [70–76].

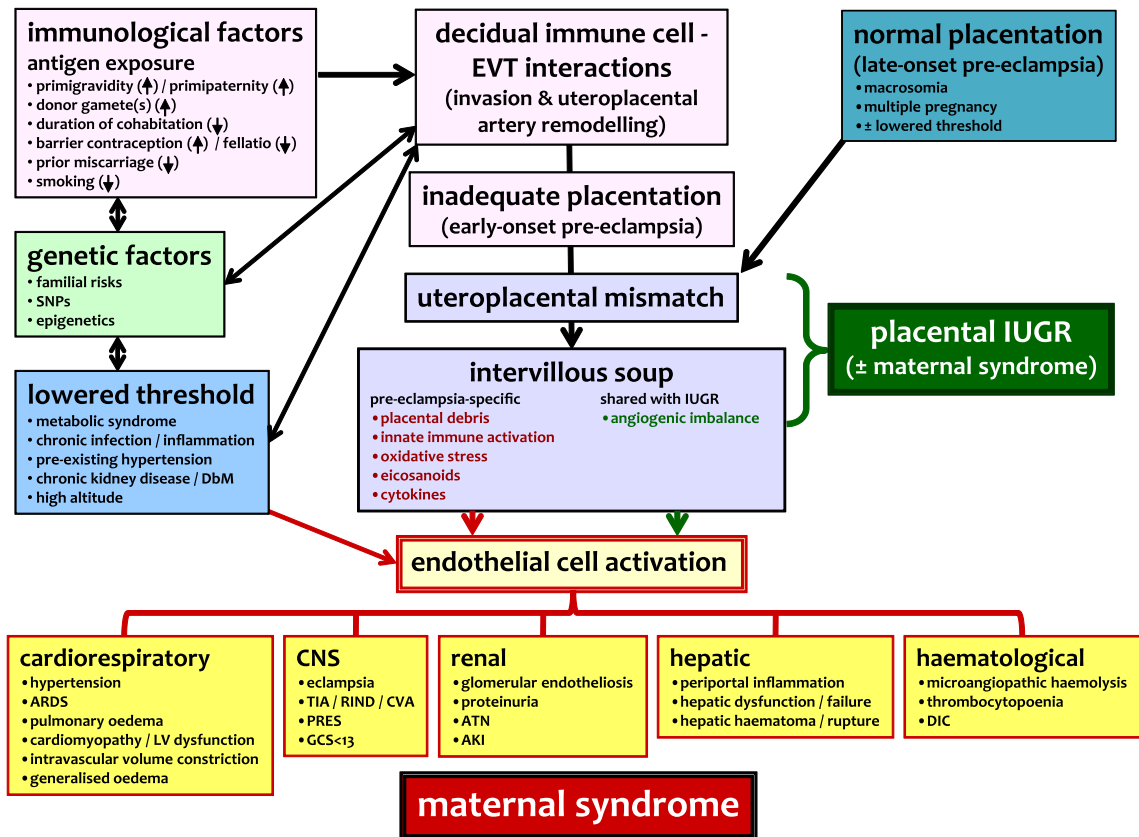
Fetal manifestations may occur before, with, or in the absence of maternal manifestations [77], and consist of oligohydramnios, IUGR (up to 30%) [78], abnormal umbilical artery Doppler velocimetry, decreased fetal middle cerebral artery resistance, an abnormal ductus venosus waveform, and/or stillbirth.

#### ○ Definition of preeclampsia

Preeclampsia is most commonly defined by new-onset proteinuria and potentially, other end-organ dysfunction. Hypertension and proteinuria are discussed under '*Diagnosis of hypertension*' and '*Proteinuria*'. Women with preeclampsia may have a diminished or no nocturnal BP decrease [10]. Table 2 outlines the end-organ dysfunction of preeclampsia: 'adverse conditions' and 'severe complications.' '**Adverse conditions**' consist of maternal symptoms, signs, and abnormal laboratory results, and abnormal fetal monitoring results that may herald development of **severe maternal or fetal complications** (including stillbirth). The 'adverse conditions' are those that we *wait for and respond to* (e.g., low oxygen saturation) to avoid the severe complications that we wish to avoid entirely (e.g., pulmonary oedema). That response could be more intensive maternal or fetal monitoring, specific treatment, or delivery. Severe maternal complications of preeclampsia warrant delivery.

#### • The adverse conditions

These are preeclampsia manifestations that increase the risk of adverse maternal or perinatal outcomes [87,95] Table 2 lists the adverse conditions by maternal organ



**Fig. 1.** The origins and consequences of preeclampsia. In this model of the origins of preeclampsia, we describe preeclampsia that arises primarily due to imperfect placentation (early-onset or 'placental' preeclampsia [pink]) and that arises due to either a lowered maternal threshold or excessive physiological placentation (late-onset or 'maternal' preeclampsia [blue]). Some aspects of the preeclampsia process are specific to it, while others are shared with normotensive intrauterine growth restriction. A lowered maternal threshold may influence the development of early-onset preeclampsia as well through direct endothelial cell activation. The consequences of the endothelial cell activation that appears consistent between all women who develop preeclampsia include a variable impact on multiple vulnerable organ systems. Disease severity generally correlates with the degree and number of organ dysfunctions. ARDS: acute respiratory distress syndrome; AKI: acute kidney injury; ATN: acute tubular necrosis; DbM: diabetes mellitus; DIC: disseminated intravascular coagulation; GCS: Glasgow Coma Scale; IUGR: intrauterine growth restriction; LV: left ventricular; PRES: posterior reversible encephalopathy syndrome; RIND: reversible ischaemic neurological deficit; SNP: single nucleotide polymorphism; TIA: transient ischaemic attack. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

system. Of particular importance are: preterm preeclampsia, chest pain or dyspnoea, or an abnormality of one/more of: oxygen saturation by pulse oximetry, platelet count, serum creatinine, or aspartate transaminase (AST) [87,95]. Proteinuria predicts neither short-term adverse outcomes nor long-term maternal renal prognosis [88,89]. HELLP syndrome is represented by its component parts; as we react to HELLP to prevent complications, rather than seeking to avoid its occurrence.

How *maternal* adverse conditions may predict *fetal or neonatal* outcomes in preeclampsia is unclear. The perinatal literature suggests that abnormal fetal monitoring of various types may identify increased fetal risk. Abnormalities in the NST should not be ascribed to antihypertensive therapy [90]. Computerized NST improves perinatal outcomes compared with visual interpretation in high risk pregnancies [91]. Oligohydramnios was not predictive of adverse outcome in observational studies of preterm preeclampsia [92]. However, oligohydramnios and abnormalities of Doppler velocimetry of the umbilical artery have

been predictive of stillbirth [86]. The biophysical profile (BPP) has unproven utility in high risk women [67,93] and BPP may falsely reassure with early-onset IUGR [94] or preeclampsia [95].

Currently, there is no single fetal monitoring test to accurately predict fetal compromise in women with preeclampsia. Most experts suggest a combination of tests, with emphasis on umbilical artery Doppler when there is IUGR [67,96].

Other non-specific risk factors for severe complications of preeclampsia are: immigrant status, young maternal age, nulliparity, lower maternal weight, and in the index pregnancy, multiple pregnancy and early-onset preeclampsia [97].

#### • What is severe preeclampsia?

Definitions vary; most include multi-organ involvement [3,98–100]. We modified our definition of severe preeclampsia to be preeclampsia associated with a severe

**Table 2**  
Adverse conditions and severe complications of preeclampsia.

Organ system affected	Adverse conditions (that increase the risk of severe complications)	Severe complications (that warrant delivery)
<b>CNS</b>	○ Headache/visual symptoms	○ Eclampsia ○ PRES ○ Cortical blindness or retinal detachment ○ Glasgow coma scale < 13 ○ Stroke, TIA, or RIND
<b>Cardiorespiratory</b>	○ Chest pain/dyspnoea ○ Oxygen saturation < 97% [79]	○ Uncontrolled severe hypertension (over a period of 12hr despite use of three antihypertensive agents), ○ Oxygen saturation < 90%, need for ≥ 50% oxygen for > 1hr, intubation (other than for Caesarean section), pulmonary oedema ○ Positive inotropic support ○ Myocardial ischaemia or infarction
<b>Haematological</b>	○ Elevated WBC count ○ Elevated INR or aPTT [80] ○ Low platelet count	○ Platelet count < 50x10 <sup>9</sup> /L ○ Transfusion of any blood product
<b>Renal</b>	○ Elevated serum creatinine [81] ○ Elevated serum uric acid	○ Acute kidney injury (creatinine > 150 μM with no prior renal disease) ○ New indication for dialysis
<b>Hepatic</b>	○ Nausea or vomiting ○ RUQ or epigastric pain ○ Elevated serum AST, ALT, LDH, or bilirubin ○ Low plasma albumin [82]	○ Hepatic dysfunction (INR > 2 in absence of DIC or warfarin) ○ Hepatic haematoma or rupture
<b>Feto-placental</b>	○ Non-reassuring FHR ○ IUGR [83,84] ○ Oligohydramnios ○ Absent or reversed end-diastolic flow by Doppler velocimetry	○ Abruptio with evidence of maternal or fetal compromise ○ Reverse ductus venosus A wave [85,86] ○ Stillbirth

AST, aspartate aminotransferase; ALT, alanine aminotransferase; DIC, disseminated intravascular coagulation; FHR, fetal heart rate; LDH, lactate dehydrogenase; PRES, posterior reversible leukoencephalopathy syndrome; RIND, reversible neurological deficit < 48hr; RUQ, right upper quadrant; TIA, transient ischaemic attack.

complication(s). **Severe preeclampsia now warrants delivery regardless of gestational age.** Our definition excludes heavy proteinuria and HELLP syndrome which is not an absolute indication for delivery.

*Other.* A 'transient' hypertensive effect is not associated with an increased risk of adverse outcomes.

White coat effect in early pregnancy (~30%) is common [19]. Forty percent of women progress to persistent hypertension at ≥20 weeks (i.e., gestational hypertension) and 8% to preeclampsia. Women with 'white coat' effect have risks (e.g., severe hypertension, preterm delivery, and NICU admission) intermediate between normotension and either pre-existing or gestational hypertension [15,60,66, 101–103].

Masked hypertension in early pregnancy (~30%) is also common [19], but associated perinatal risks are unknown. Outcomes with masked hypertension at ≥20 weeks (~10%) equate to gestational hypertension [104,105]. Masked hypertension could be considered (and ABPM/HBPM performed) if there are unexplained maternal or perinatal complications typically associated with the HDPs.

#### Investigations to classify HDP

#### Recommendations

1. For women with pre-existing hypertension, the following should be performed in early pregnancy (if not

previously documented): serum creatinine, fasting blood glucose, serum potassium, and urinalysis (III-D; Low/Weak) and EKG (II-2C; Low/Weak).

2. Among women with pre-existing hypertension or those with a strong clinical risk marker for preeclampsia, additional baseline laboratory testing may be based on other considerations deemed important by health care providers. (III-C; Very low/Weak).
3. Women with suspected preeclampsia should undergo the maternal laboratory (II-2B; Moderate/Strong) and pertinent fetal (II-1B; Moderate/Strong) testing described in (Table 3).
4. Doppler velocimetry-based assessment of the fetal circulation may be useful to support a placental origin for hypertension, proteinuria, and/or adverse conditions (including IUGR) (II-2B; Moderate/Weak) and for timing of delivery (IA; High/Strong).
5. There is insufficient evidence to recommend use of the biophysical profile (BPP) as part of a schedule of fetal testing in women with a HDP (II-2I; Moderate/Weak).
6. If initial testing is reassuring, maternal and fetal testing should be repeated if there is ongoing concern about preeclampsia (e.g., change in maternal and/or fetal condition) (III-C; Low/Weak).

#### Comments

*Pre-existing hypertension.* More than 95% of these women have essential hypertension. We support the Canadian Hypertension Education Program (CHEP) work-up (see

**Table 3**

Investigations to diagnosis or monitor women with a HDP.

Investigations for diagnosis	Description in women with preeclampsia	Description in women with other conditions
<i>Maternal testing</i>		
<b>Urine testing</b>		
Urinalysis (routine and microscopy with/without additional tests for proteinuria)	Proteinuria (as discussed under <i>Proteinuria</i> ) without RBCs or casts	Haemoglobinuria (dipstick 'haematuria' without RBCs): haemolytic anaemia RBCs alone: renal stones, renal cortical necrosis (also associated with back pain and oliguria/anuria) RBCs and/or casts are associated with other glomerular disease and scleroderma renal crisis and (about half of) TTP-HUS Bacteria: UTI or asymptomatic bacteriuria Proteinuria is usually absent in secondary causes of hypertension such as pheochromocytoma, hyperaldosteronism, thyrotoxicosis, coarctation of the aorta, and withdrawal syndromes
<b>Oxygen saturation</b>		
Pulse oximetry	SpO <sub>2</sub> < 97% associated with a heightened risk of severe complications (including non-respiratory)	May be decreased in any cardiorespiratory complication (e.g., pulmonary embolism)
<b>CBC and blood film</b>		
Haemoglobin	↑ due to intravascular volume depletion ↓ if microangiopathic haemolysis (with HELLP)	↑ due to volume depletion from any cause (e.g., vomiting) ↓ if microangiopathic haemolysis from other cause ↓ with any chronic anaemia (nutritional or myelodysplasia) ↓ with acute bleeding of any cause
WBC and differential	↔	↑ due to neutrophilia of normal pregnancy ↑ with inflammation/infection ↑ with corticosteroids
Platelet count	↓ – associated with adverse maternal outcome)	↓ with gestational, immune (ITP), or thrombotic thrombocytopenia (TTP), APS, AFLP, myelodysplasia
Blood film	RBC fragmentation	Microangiopathy due to mechanical causes (e.g., cardiac valvopathy, cavernous haemangioma), DIC or other disorders of endothelial function (e.g., APS, TTP-HUS, vasculitis, malignant hypertension)
<b>Tests of coagulation*</b>		
INR and aPTT	↑ with DIC which is usually associated with placental abruption – ↑ is associated with adverse maternal outcome	May be ↑ in APS, DIC from other causes including sepsis, amniotic fluid embolism, stillbirth, massive haemorrhage, haemangiomas, shock ↑ is prominent in AFLP ↓ with all causes of DIC including massive haemorrhage, genetic disorders ↓ more profound with AFLP than with HELLP Usually normal in TTP-HUS (ADAMTS13 vWF cleaving protein may be moderately decreased in HELLP [109] but ADAMTS 13 antibody should be absent)
Fibrinogen	↔	
<b>Serum chemistry</b>		
Serum creatinine	↑ due to haemoconcentration and/or renal failure – ↑ associated with adverse maternal outcome	↑ with other acute or chronic kidney disease  Renal failure prominent in malignant hypertension, TTP-HUS (along with thrombocytopenia), AFLP (along with liver dysfunction)
Serum uric acid	↑ – associated with adverse maternal and perinatal outcomes	↑ with dehydration, medication (e.g., HCTZ), genetic causes
Glucose	↔	↓ with AFLP, insulin therapy
AST or ALT	↑ – associated with adverse maternal outcome	↑ with AFLP and other 'PET imitators' <sup>†</sup> but to a lesser degree, and usually normal in TTP-HUS May be increased in other pregnancy-related conditions (e.g., intrahepatic cholestasis of pregnancy) or conditions not associated with pregnancy (e.g., viral hepatitis or cholecystitis)
LDH	↑ which may be prominent – the ↑ is associated with adverse maternal outcome	↑ with AFLP, intravascular haemolysis
Bilirubin	↑ – unconjugated from haemolysis or conjugated from liver dysfunction	↑ LDH/AST ratio (>22) with TTP-HUS [110] (early) ↑ in AFLP, ↑ with haemolytic anaemia, other liver disease with dysfunction, genetic diseases
Albumin	↓ – associated with adverse maternal and perinatal outcomes	↓ as negative acute phase reactant with acute severe illness, malnutrition, nephrotic syndrome, crystalloid infusion
<i>fetal testing</i>		
Uterine artery Doppler velocimetry <sup>‡</sup>	Abnormalities are not specific to the cause of poor placentation and/or placental dysfunction Unilateral/bilateral notching, or elevated pulsatility index or resistance index may support a diagnosis of placental insufficiency including preeclampsia	

Table 3 (continued)

Investigations for diagnosis	Description in women with preeclampsia	Description in women with other conditions
Fetal monitoring	Abnormal or atypical FHR tracing (e.g., decreased variability)	
Deepest amniotic fluid pocket	Oligohydramnios associated with adverse perinatal outcomes [98]	
Ultrasonographic assessment of fetal growth	Usually intrauterine fetal growth restriction (typically asymmetrical but can be symmetrical if early and/or severe)	
Umbilical artery Doppler	Increased resistance, absent or reversed end-diastolic flow	
Ductus venosus Doppler	Increased resistance, especially absent or reversed "a" wave	
Middle cerebral artery Doppler	Cerebral redistribution (decreased resistance, or "brain sparing effect"). May be lost in extreme cases prior to fetal death	

AFLP, acute fatty liver of pregnancy; APS, antiphospholipid antibody syndrome; CBC, complete blood count; DIC, disseminated intravascular coagulation; FHR, fetal heart rate; HELLP, haemolysis, elevated liver enzyme, low platelet syndrome; TTP-HUS, thrombotic thrombocytopenic purpura – haemolytic uraemic syndrome; PET, preeclampsia-eclampsia; SpO<sub>2</sub>, oxygen saturation; UTI, urinary tract infection; vWF, von Willebrand Factor.

‡ Abnormal uterine artery Doppler velocimetry is practically defined at 22–24 weeks as bilateral notching with mean resistance index (RI) > 0.55 (i.e., > 50th centile), unilateral notching with mean RI > 0.65 (> 90th centile), or no notching with mean RI > 0.70 (>95th centile) [163].

\* Tests of coagulation are recommended if there is thrombocytopenia [80] or placental abruption.

† PET imitators' include AFLP, catastrophic APS, TTP-HUS, malignant hypertension and scleroderma renal crisis.

CHEP guidelines [7]). Relevant baseline testing in early pregnancy may be prudent with chronic conditions (e.g., non-alcoholic steatohepatitis) that may make subsequent interpretation of end-organ dysfunction difficult. Women at high risk for preeclampsia should be assessed for baseline proteinuria (e.g., spot PrCr) given the insensitivity of dipstick testing. Fasting blood glucose  $\geq 7$  mM pre-pregnancy or  $\geq 5.3$  mM in pregnancy should prompt appropriate investigation/referral [106,107]. An abnormal P wave in lead V1 by EKG may increase risk for gestational hypertension or preeclampsia [108]. Echocardiography may be useful with known/suspected left ventricular dysfunction or heart failure [7]. Routine measurement of plasma lipids is not advised.

*When preeclampsia is suspected.* Women with suspected preeclampsia should undergo blood and urine testing (Table 3) [112–118] designed to either: (i) detect end-organ involvement that increases the risk of adverse outcomes, (ii) detect adverse outcomes (e.g., acute renal failure), (iii) evaluate the seriousness of adverse outcome (e.g., haemoglobin with abruption), or (iv) explore important differential diagnoses. Information collected will inform timing of delivery.

Most abnormalities of maternal and fetal testing are non-specific. Interpretation relies on multiple (not single) abnormalities. With ongoing suspicion of preeclampsia, a change in maternal or fetal status should prompt repeat testing. Abnormalities of Doppler-based assessment of the uterine or fetal circulations warrant obstetric consultation as they reflect elevated risks of adverse outcomes and results may inform timing of delivery [119–126]. Consultation may be practically limited to telephone. The BPP does not improve, and may adversely affect, high risk pregnancy outcomes [93,95].

Preeclampsia imitators share manifestations with preeclampsia, but require different treatments (Table 4) [127–131].

*Biomarkers for the diagnosis of preeclampsia: Imminent developments.* A minority of women with preeclampsia will have an unclear clinical diagnosis, in which case translational biomarkers may improve diagnostic accuracy. Leading biomarkers reflect the angiogenic imbalance that,

although not specific to preeclampsia [132], may underlie many of its maternal features (particularly with early-onset) [133,134]. Two platforms measuring placental growth factor (PlGF) and soluble FMS-like tyrosine kinase-1 (sFlt-1), either singly (i.e., PlGF) or as a ratio (e.g., sFlt-1/PlGF ratio) [134,135] are being licenced in North America.

## Chapter 2: Prediction and prevention

### Predicting preeclampsia

#### Recommendations

1. Women should be screened for clinical risk markers of preeclampsia from early pregnancy (II-2 C; Low/Strong).
2. Consultation with an obstetrician or an obstetric internist, by telephone if necessary, should be considered for women with a history of previous preeclampsia or another strong clinical marker of increased preeclampsia risk, particularly multiple pregnancy, antiphospholipid antibody syndrome, significant proteinuria at booking, or a pre-existing condition of hypertension, diabetes mellitus, or renal disease (II-2 B; Very low/Strong).
3. Screening using biomarkers or Doppler ultrasound velocimetry of the uteroplacental circulation cannot be recommended routinely at present for women at low or increased risk of preeclampsia until such screening has been shown to improve pregnancy outcome (II-2C; Very low/Weak).

#### Comments

Of the many risk markers for preeclampsia (Table 5) [99,111,136–164], many are known at booking and increase the risk of preeclampsia two- to fourfold [165]. The strongest of these are previous preeclampsia, antiphospholipid antibody syndrome, pre-existing medical conditions, and multiple pregnancy (all bolded in Table 5). For other risk markers, the strength of the association is less well established, less consistent, or the marker becomes available in the second or third trimesters (see below).

**Table 4**  
Preeclampsia imitators.

Pregnancy related	Not pregnancy related
Preeclampsia/HELLP syndrome	Malignant hypertension regardless of the cause
Acute fatty liver of pregnancy	Secondary causes of hypertension when associated with end-organ involvement (e.g., renal disease, pheochromocytoma)
	Disseminated intravascular coagulation (from any cause)
	Thrombotic thrombocytopenic purpura
	Haemolytic uraemic syndrome
	Vasculitis or other systemic rheumatic condition (systemic lupus erythematosus, scleroderma, cryoglobulinemia, catastrophic antiphospholipids syndrome)
	Sepsis
	Medications
	Cavernous hemangiomas
	Malignancy

HELLP, Haemolysis, Elevated Liver enzyme, Low Platelet syndrome.

*Previous preeclampsia.* With prior preeclampsia (of any type), the risk of recurrent preeclampsia in a subsequent pregnancy varies widely (median 15%) [169–191], as does “severe” recurrent preeclampsia (median 15%) [170,175,176,181,182,184,188,192–195]. Recurrence is more likely when prior preeclampsia was: of early onset [184,188,194], “severe” [169,187], or complicated by eclampsia [192,193,196] or HELLP syndrome [176,177,182,188]. Higher BMI in prior preeclampsia increases the recurrence risk [185]. The following traditional preeclampsia risk markers for *first occurrence* do not influence *recurrence*: multiple gestation, change of partner, and long interpregnancy interval) [179,184,197–199].

Women with prior preeclampsia are as likely to have gestational hypertension (median 22%) as preeclampsia (median 15%) in their next pregnancy. Women with prior gestational hypertension are more likely to experience gestational hypertension in their next pregnancy (median 21%) than preeclampsia (median 4%) [169,171–173].

*Screening for preeclampsia (in women with or without a history of a HDP).* The strongest clinical markers of preeclampsia risk identifiable at antenatal booking are recommended for screening for preeclampsia in the community [145]. Women can be offered subspecialty referral, and must receive more frequent assessments, if they have one strong risk factor (bolded in Table 5), or two or more minor risk factors (Table 5).

Of nine **clinical** predictors of preeclampsia among nulliparous women carrying singleton pregnancies, one is protective (miscarriage at  $\leq 10$  weeks with same partner) and eight increase risk (younger maternal age, higher MAP, higher BMI, family history of preeclampsia or coronary heart disease, woman with lower birthweight, vaginal bleeding during early pregnancy, and short duration of sexual relationship); half of women destined to develop preeclampsia would be detected using the model [162].

First trimester uterine artery Doppler, shows promise but needs further ‘real life’ evaluation [200].

Markers of preeclampsia risk that become available in the second and third trimesters include measures of: placental perfusion, vascular resistance, and morphology (e.g., mean maternal second trimester BP, 24-h ABPM, Doppler); maternal cardiac output and systemic vascular

resistance; fetoplacental unit endocrinology [e.g., pregnancy-associated plasma protein-A (PAPP-A) in the first trimester, and alpha-fetoprotein, hCG, and inhibin-A in the early second trimester]; maternal renal function (e.g., serum uric acid or microalbuminuria); maternal endothelial function and endothelial–platelet interaction (e.g., platelet count, antiphospholipid antibodies, or homocysteine); oxidative stress (e.g., serum lipids); and circulating angiogenic factors [201–203].

Systematic reviews of primary studies have evaluated clinically available biomarkers [163,164,204] and no single clinical test reaches the ideal of  $\geq 90\%$  sensitivity for preeclampsia prediction. Only uterine artery Doppler at 20–24 weeks has sensitivity  $>60\%$  for detection of preeclampsia, particularly when testing is performed: (i) in women at increased risk of preeclampsia; (ii) during the second trimester, and/or (iii) when predicting severe and early preeclampsia. Women with abnormal velocimetry could be considered for increased surveillance to detect preeclampsia or other adverse placental outcomes. Uterine artery Doppler should not be used in low risk women [162,205].

It is unclear whether markers used for Down syndrome screening are useful in isolation (or with uterine artery Doppler) for preeclampsia prediction [206].

Thrombophilia screening is not recommended for investigation of prior preeclampsia or other placental complications, except if the woman satisfies the *clinical* criteria for the antiphospholipid antibody syndrome [207,208].

As no single test predicts preeclampsia with sufficient accuracy to be clinically useful [209], interest has grown in researching multivariable models that include clinical and laboratory predictors available at booking and thereafter [166,209,210]. Clinicians should support clinics conducting relevant prospective longitudinal studies.

#### *Preventing preeclampsia and its complications*

We have based our recommendations on both prevention of preeclampsia and/or its associated complications.

Pregnant women have been classified as being at ‘low’ or ‘increased’ risk of preeclampsia, usually by the presence of one or more risk markers as shown in Table 5 [see *Prediction*].

**Table 5**  
Risk markers for preeclampsia.\*

Demographics and family history	Past medical or obstetric history	Current pregnancy	
		First trimester	Second or third trimester
	<b>Previous preeclampsia</b> <b>Anti-phospholipid antibody syndrome</b> <b>Pre-existing medical condition(s)</b> <ul style="list-style-type: none"> <li>• Pre-existing hypertension or booking diastolic BP <math>\geq</math> 90 mmHg</li> <li>• Pre-existing renal disease or booking proteinuria</li> <li>• Pre-existing diabetes mellitus</li> </ul>	<b>Multiple pregnancy</b>	
Maternal age <sup>‡</sup> $\geq$ 40 years	Lower maternal birthweight and/or preterm delivery	Overweight/obesity	Elevated BP (gestational hypertension) <sup>†</sup>
Family history of preeclampsia (mother or sister)	Heritable thrombophilias <sup>‡</sup>	First ongoing pregnancy	Abnormal AFP, hCG, inhA or E <sub>3</sub> <sup>***</sup>
Family history of early-onset cardiovascular disease	Increased pre-pregnancy triglycerides	New partner	Excessive weight gain in pregnancy
	Non-smoking	Short duration of sexual relationship with current partner	Infection during pregnancy (e.g., UTI, periodontal disease)
	Cocaine and amphetamine use	Reproductive technologies <sup>**</sup>	Abnormal uterine artery Doppler IUGR
	Previous miscarriage at $\leq$ 10 weeks with same partner	Inter-pregnancy interval $\geq$ 10 years	Investigational laboratory markers <sup>#</sup>
		Booking sBP $\geq$ 130 mmHg, or booking dBP $\geq$ 80 mmHg	
		Vaginal bleeding in early pregnancy	
		Gestational trophoblastic disease	
		Abnormal PAPP-A or free $\beta$ hCG	
		Investigational laboratory markers	

AFP, alfafetoprotein; E<sub>3</sub>, oestriol; hCG, human chorionic gonadotropin; inhA, inhibin A; IUGR, intrauterine fetal growth restriction; MSS, maternal serum screening; PAPP-A, pregnancy-associated plasma protein A; UTI, urinary tract infection.

\* Maternal age was considered as a continuous variable in the SCOPE study [162].

\* Women at increased risk (who should be considered for specialty referral) are those with one of the bolded factors, or two or more of the unbolded markers [139].

\*\* Subfertility and its treatment (especially the use of donor eggs, sperm and/or gametes), after correction for multiple gestations.

\*\*\* Decreased first trimester PAPP-A (pregnancy-associated plasma protein A)  $\leq$ 5th centile [141], decreased first or second trimester PIGF (placental growth factor) [154–156], unexplained increased second trimester AFP (alfafetoprotein) [142–147], increased second trimester hCG [145–148], increased first or second trimester inhibin A [144,149–152], increased second trimester activin. [153]. Abnormal uterine artery Doppler velocimetry is practically defined at 22–24 weeks as bilateral notching with mean resistance index (RI)  $>$  0.55 (i.e.,  $>$ 50th centile), unilateral notching with mean RI  $>$  0.65 ( $>$ 90th centile), or no notching with mean RI  $>$  0.70 ( $>$ 95th centile) [164].

<sup>†</sup> Elevated BP is defined as dBP  $\geq$  110 mmHg before 20 weeks, 2nd trimester mean arterial pressure of  $\geq$ 85 mmHg, or a 2nd trimester sBP  $\geq$  120 mmHg [140] standardized cut-offs for 24-h ambulatory BP or home BP monitoring have not been established.

<sup>‡</sup> Heritable thrombophilia includes Factor V Leiden gene mutation and Protein S deficiency.

<sup>#</sup> Investigational markers include, in the first trimester: PAPP-A, PIGF, PP-13 [167,168], and in the second trimester: elevated sFlt-1/PIGF (soluble fms-like tyrosine kinase, placental growth factor) [155–157], PAI-1/PAI-2 (plasminogen activator inhibitor) [157], von Willebrand factor, and leptin [154,157,158].

Preventative interventions may be best started before 16 weeks when most of the physiologic transformation of uterine spiral arteries occurs. Such early intervention has the greatest potential to decrease early forms of preeclampsia [211].

#### Preventing preeclampsia and its complications in women at low risk

Women at 'low risk' of preeclampsia have usually been from unselected populations of nulliparous and multiparous women.

#### Recommendations

1. Calcium supplementation (of at least 1 g/d, orally) is recommended for women with low dietary intake of calcium ( $<$ 600 mg/d) (I-A; High/Strong).
2. The following are recommended for other established beneficial effects in pregnancy: abstinence from alcohol for prevention of fetal alcohol effects (II-2E; Low/Strong), exercise for maintenance of fitness (I-A; Moderate/Strong), periconceptual use of a folate-containing multivitamin for prevention of neural tube defects (I-A; Moderate/Strong), and smoking cessation for prevention of low birthweight and preterm birth (I-E; High/Strong).
3. The following may be useful: periconceptual and ongoing use of a folate-containing multivitamin (I-B; Low/Weak), or exercise (II-2B; Very low/Weak).
4. The following are **not** recommended for preeclampsia prevention, but may be useful for prevention of other pregnancy complications: prostaglandin precursors (I-C; Low/Weak), or supplementation with magnesium (I-C; Low/Weak), or zinc (I-C; Low/Weak).

5. The following are **not** recommended: dietary salt restriction during pregnancy (I-D; Moderate/Strong), calorie restriction during pregnancy for overweight women (I-D; Moderate/Strong), low-dose aspirin (I-E; Moderate/Weak), vitamins C and E (based on current evidence) (I-E; High/Strong), or thiazide diuretics (I-E; Moderate/Strong).
6. There is insufficient evidence to make a recommendation about the following: a heart-healthy diet (II-2L; Very low/Weak), workload or stress reduction (which includes bedrest) (II-2L; Very low/Weak), supplementation with iron with/without folate (I-L; Low/Weak), vitamin D (I-L; Very low/Weak), pyridoxine (I-L; Low/Weak), or food rich in flavonoids (I-L; Very low/Weak).

#### Comments

**Abstinence from alcohol.** The effect of alcohol abstinence on the incidence of HDPs is unknown, although reduced consumption reduces BP outside pregnancy [212]. There is no proven safe level of alcohol consumption in pregnancy [213].

**Aspirin (low-dose).** Low dose aspirin does not decrease preeclampsia incidence in low risk nulliparous women (RR 0.93; 95% CI 0.81–1.08) [204,214–217], although first trimester aspirin initiation is untested in RCTs.

**Calcium.** Oral calcium supplementation (of at least 1 g/d) decreases the incidence of preeclampsia (RR 0.45, 95% CI 0.31–0.65) and gestational hypertension (RR 0.71, 95% CI 0.57–0.89) [218,219]. Maternal death or serious morbidity was reduced (RR 0.80; 95% CI 0.65–0.97) [220], more than offsetting the possible increase in HELLP (RR 2.67, 95% CI 1.05–6.82); it is possible that the BP lowering effect of calcium masks progression to HELLP [221]. The benefits of calcium are probably restricted to women with low calcium intake (<600 mg/day) [219]; potential harms (e.g., osteoporosis during lactation) have not been excluded [222]. An alternative to supplementation may be 3–4 dairy servings/day (250–300 mg calcium/serving).

**Dietary changes.** Dietary salt restriction does not affect gestational hypertension or preeclampsia incidence (RR 1.11; 95% CI 0.46–2.66) [223]. Heart healthy diets are untested.

Energy or protein restriction diets for overweight women or those with excessive pregnancy weight gain did not decrease gestational hypertension or preeclampsia incidence [224]. Starvation ketosis may adversely alter fetal neurodevelopment [225].

Consuming milk-based probiotics may lower preeclampsia risk (population-based cohort) [226]; no RCT was identified.

One RCT found a significant reduction of BP with daily intake of high-cocoa-content chocolate from 11 to 13 weeks until delivery [227]. Two RCTs are studying the impact of flavanol-rich chocolate on endothelial function and the risk of preeclampsia (ClinicalTrials.gov NCT01659060), (ClinicalTrials.gov NCT01431443).

**Folate-containing multivitamins.** Periconceptual use of a folate-containing multivitamin is recommended for all

women for primary prevention of neural tube and possibly other anomalies [228]. Periconceptual and ongoing regular use of multivitamins may prevent gestational hypertension [229] and preeclampsia in women with a BMI < 25 kg/m<sup>2</sup> [230].

**Lifestyle changes.** Moderate-intensity regular aerobic exercise (vs. normal physical activity) during pregnancy did not decrease preeclampsia or other adverse outcomes [231]. Although workload/stress reduction is a common obstetric intervention, no relevant RCTs were identified that tested the impact on preeclampsia incidence.

**Micronutrients other than calcium.** Using generally low quality data, magnesium supplementation (primarily in low risk women) did not affect HDP incidence, but did decrease preterm birth (RR 0.73, 95% CI 0.57–0.94), low birthweight (RR 0.67, 95% CI 0.46–0.96), and SGA infants (RR 0.70, 95% CI 0.53–0.93) [232].

Zinc supplementation (20–90 mg elemental zinc), primarily in low income low risk women did not affect HDP incidence, but did decrease preterm delivery (RR 0.86; 95% CI 0.76–0.97) [233].

**Prostaglandin precursors.** Marine and other oils (prostaglandin precursors) do not decrease preeclampsia risk in mixed populations of low and high risk women (RR 0.86, 95% CI 0.59–1.27), but do decrease birth before 34 weeks (RR 0.69, 95% CI 0.49–0.99) [234]. Increased dietary intake of fish for marine oil consumption is not recommended because of concerns about heavy metals [235].

**Smoking cessation.** Smoking cessation is recommended to decrease low birthweight (RR 0.81; 95% CI 0.70–0.94) and preterm birth (RR 0.84; 95% CI 0.72–0.98) [236]. Nicotine replacement therapy in pregnancy neither improves quit rates in pregnancy nor alters adverse outcomes [237].

**Thiazide diuretics.** Thiazide diuretics do not decrease preeclampsia (RR 0.68; 95% CI 0.45–1.03) or other substantive outcomes [238].

**Vitamins C and E.** Vitamins C and E from the first or early second trimester may have actually increased preeclampsia, preterm prelabour rupture of membranes, IUGR, and perinatal death [239–241].

**Vitamin D.** Low levels of 25 hydroxy vitamin D have been associated with an increase in preeclampsia and other adverse placental outcomes. There is insufficient evidence to recommend supplemental vitamin D (above the recommended daily allowance of 400–1000 IU/d) for preeclampsia prevention or improving pregnancy outcome otherwise [242].

**Other interventions for which no recommendation can be made.** There is insufficient (or no) evidence on the effect on preeclampsia of supplementation with: iron (routinely, or not, or routinely with/without folic acid) [243], pyridoxine [244], garlic, vitamin A, selenium, copper, or iodine.

### Preventing preeclampsia and its complications in women at increased risk

Women at 'increased risk' of preeclampsia are most commonly identified by a personal or family history of a HDP, chronic medical disease, and/or abnormal uterine artery Doppler before 24 weeks. Combining clinical, biochemical, and/or ultrasonographic risk markers may better identify women at increased preeclampsia risk (see *Prediction*); however, no intervention trial has used such an approach to evaluate preventative therapy [167,168,245].

#### Recommendations

1. The following are recommended for prevention of preeclampsia: low-dose aspirin (I-A; High/Strong) and calcium supplementation (of at least 1 g/d) for women with low calcium intake (I-A; High/Strong).
2. Aspirin should be: taken in a low dose (75–162 mg/d) (III-B; Very low/Strong), administered at bedtime (I-B; Moderate/Strong), initiated after diagnosis of pregnancy but before 16 weeks' gestation (I-B; Low/Weak), and considered for continuation until delivery (I-C; Very low/Weak).
3. Prophylactic doses of LMWH may be discussed in women with previous placental complications (including preeclampsia) to prevent the recurrence of 'severe' or early-onset preeclampsia, preterm delivery, and/or SGA infants (I-B; Moderate/Weak).
4. The following may be useful: L-arginine (I-B; Moderate/Weak), increased rest at home in the third trimester (I-C; Low/Weak), and reduction of workload or stress (III-C; Very low/Weak).
5. The following may be useful for prevention of other pregnancy complications: prostaglandin precursors (I-B; Low/Weak), magnesium supplementation (I-C; Low/Weak), and heparin to prevent venous thromboembolic disease (I-B; Low/Weak).
6. The following are recommended for other established beneficial effects in pregnancy (as discussed for women at low risk of preeclampsia): abstinence from alcohol (II-2E; Low/Strong), periconceptual use of a folate-containing multivitamin (I-A; Moderate/Strong), and smoking cessation (I-E; High/Strong).
7. The following are **not** recommended: calorie restriction in overweight women during pregnancy (I-D; Low/Weak), weight maintenance in obese women during pregnancy (III-D; Very low/Weak), antihypertensive therapy specifically to prevent preeclampsia (I-D; Moderate/Strong), vitamins C and E (I-E; High/Strong).
8. There is insufficient evidence to make a recommendation about the usefulness of the following: the heart-healthy diet (III-L; Very low/Weak); exercise (I-L; Very low/Weak); selenium (I-L; Very low/Weak); garlic (I-L; Very low/Weak); zinc, pyridoxine, iron (with or without folate), vitamin D, or multivitamins with/without micronutrients (all III-L; all Very low/Weak).

#### Comments

*Antihypertensive therapy.* Antihypertensive therapy does not prevent preeclampsia (RR 0.99; 95% CI 0.84–1.18) or

adverse outcomes, but halves the risk of severe hypertension (RR 0.52; 95% CI 0.41–0.64) [246–248]. It is unknown whether this is outweighed by a negative impact on perinatal outcomes [61] (see *Treatment, Antihypertensive Therapy*).

*Aspirin (low dose).* In women at increased risk of preeclampsia, low-dose aspirin results in a small decrease in: preeclampsia (RR 0.83; 95% CI 0.77–0.89; NNT 72; 95% CI 52–119), preterm delivery (RR 0.92, 95% CI 0.88–0.97; NNT 72, 95% CI 52–119), SGA infants (RR 0.90, 95% CI 0.83 to 0.98; NNT 114, 95% CI 64–625) and perinatal death (RR 0.86, 95% CI 0.76–0.98; NNT 243; 95% CI 131–1666) without increasing bleeding risk [249].

Aspirin neither increases nor decreases miscarriage risk [250,251]. There is no evidence of teratogenicity [252] or other short- or long-term adverse paediatric effects.

Who should receive aspirin, in what dose, and when, are unclear. Aspirin is more effective in decreasing preeclampsia: (i) among high risk women (NNT 19, 95% CI 13–34), (ii) when initiated before 16 weeks [252–255], (iii) at doses >80 mg/day [249,256–259]; and (iv) when taken at bedtime [260,261]. Adjusting dosage based on platelet function testing may improve aspirin effectiveness [262]. Aspirin may be continued until delivery [263] (see *Anaesthesia and Fluid Administration*).

*Calcium.* Oral calcium supplementation (of at least 1 g/d) decreases rates of preeclampsia (RR 0.22; 95% CI 0.12–0.42), gestational hypertension (RR 0.47, 95% CI 0.22–0.97) and preterm delivery (RR 0.45; 95% CI 0.24–0.83) [218]. Three trials were conducted in low calcium intake populations but no trial included women with prior preeclampsia or reported on HELLP.

*Dietary changes.* No trials were identified of dietary salt restriction on preeclampsia incidence. Women with pre-existing hypertension following a DASH (Dietary Approaches to Stop Hypertension) diet may continue it. Heart healthy diets are untested.

Dietary counselling to curb the rate of weight gain of overweight pregnant women has no impact on gestational hypertension or preeclampsia [224]. Pre-pregnancy or early pregnancy weight reduction is untested [225].

*Folate-containing multivitamin.* Periconceptual (to prevent neural tube defects and possibly, other anomalies) and ongoing regular use of multivitamins is associated with higher birthweights [264]. The Canadian FACT Trial for preeclampsia prevention is recruiting (<http://clinicaltrials.gov/show/NCT01355159>).

*Heparin.* Prophylactic doses of any heparin (vs. no treatment), decreases perinatal mortality (2.9% vs. 8.6%; RR 0.40, 95% CI 0.20–0.78), delivery <34 weeks (8.9% vs. 19.4%; RR 0.46, 95% CI 0.29–0.73), and SGA infants (7.6% vs. 19.0%; RR 0.41, 95% CI 0.27–0.61) in women at high risk of placentally mediated complications [265]. LMWH alone (vs. no treatment) reduces the risk of: 'severe' or early-onset preeclampsia (1.7% vs. 13.4%; RR 0.16, 95% CI 0.07–0.36), preterm delivery (32.1% vs. 47.7%; RR 0.77, 95% CI

0.62–0.96), and SGA infants (10.1% vs. 29.4%; RR 0.42, 95% CI 0.29–0.59), without a significant effect on perinatal mortality (pregnancy loss >20 weeks 1.9% vs. 5.3%; RR 0.41, 95% CI 0.17–1.02) [266]. Observed decreases in preeclampsia and a composite of placentally-mediated pregnancy complications (i.e., preeclampsia, placental abruption, SGA infants, or fetal loss >12 weeks) (18.7% vs. 42.9%; RR 0.52, 95% CI 0.32–0.86) were more different than could be expected by chance alone. Pending definitive data, LMWH for preeclampsia prevention should be used cautiously. The independent role of concomitant aspirin needs clarification.

LMWH in prophylactic doses is associated with minimal maternal and, theoretically, no fetal risks as it does not cross the placenta. Major allergic reactions are uncommon (1.2%) and no studied woman developed heparin-induced thrombocytopenia. Prophylactic LMWH was rarely associated with antenatal bleeding (0.42%), intrapartum bleeding (0.92%), or wound haematoma after either Caesarean or vaginal delivery (0.65%) [267], as observed in an audit of tinzaparin use in pregnancy [268]. LMWH could be stopped at 34–36 weeks to avoid intrapartum and postpartum risk.

If LMWH were effective for prevention of placental complications, the incremental cost of preventing one case of severe preeclampsia or a SGA infant approximates \$54.00 [269].

*L-Arginine.* L-Arginine given to women with gestational hypertension, preeclampsia, or IUGR may lead to improved maternal BP and uteroplacental circulation [270–275] but dosage needs to be defined and large RCTs are required.

*Lifestyle changes.* No impact of exercise was seen on gestational hypertension or preeclampsia [231]. Among sedentary women with prior preeclampsia specifically, walking vs. stretching exercise did not alter pregnancy outcomes [276]. There is one ongoing RCT of moderate intensity exercise in women with prior preeclampsia [277].

RCT evidence is lacking for workload or stress reduction to prevent preeclampsia.

Increased rest at home (30 min to 6 h/day) in the third trimester decreases preeclampsia incidence (RR 0.05; 95% CI 0.00–0.83 for increased rest alone; RR 0.13; 95% CI 0.03–0.51 for rest plus nutritional supplement) [278]. The definition of bed rest is unclear and compliance uncertain [279].

Treatment of periodontal disease does not decrease preeclampsia [280,281].

*Micronutrients other than calcium.* Magnesium supplementation in a mixed low and high risk population did not decrease preeclampsia, but decreased preterm birth (RR 0.73; 95% CI 0.57–0.94), low birthweight (RR 0.67; 95% CI 0.46–0.96), and SGA infants (RR 0.70, 95% CI 0.53–0.93) [232]. No conclusions can be drawn because only one trial was of high quality.

Selenium supplementation in the third trimester may or may not decrease “gestational hypertension” (undefined) and preeclampsia [282,283].

Garlic has no impact on preeclampsia in women at increased preeclampsia risk based on the historical positive roll-over test [284].

Supplementation with CoQ10 from 20 weeks may reduce preeclampsia (RR 0.56, 95% CI 0.33–0.96) [285].

We did not identify relevant trials of zinc, pyridoxine, iron (with/without folic acid), multivitamins with/without micronutrients, vitamin A, vitamin D, iodine, or copper.

*Prostaglandin precursors.* Prostaglandin precursors do not decrease preeclampsia in mixed low and high risk populations (RR 0.87; 95% CI 0.59–1.28) [234], but birth <34 weeks is marginally decreased (RR 0.69; 95% CI 0.49–0.99). Fish oil supplementation in women with previous pregnancy complications showed more advanced gestational age at delivery in low and middle (but not high) fish consumers [286].

*Vitamins C and E.* After contradictory pilot trial findings [287–289], vitamins C and E do not decrease preeclampsia risk; rather, they are more frequently associated with birthweight <2.5 kg and adverse perinatal outcomes [290–293].

### Chapter 3: Treatment of the HDPs

#### Antenatal treatment

#### Non-pharmacological treatment of HDP

#### Dietary & lifestyle changes.

#### Recommendations

1. There is insufficient evidence to make a recommendation about the usefulness of the following: new severe dietary salt restriction for women with any HDP, ongoing salt restriction among women with pre-existing hypertension, heart-healthy diet, and calorie restriction for obese women (all III-L; all Very low/Weak).
2. There is insufficient evidence to make a recommendation about the usefulness of: exercise, workload reduction, or stress reduction (all III-L; all Very low/Weak).
3. For women with gestational hypertension (without preeclampsia), some bed rest in hospital (vs. unrestricted activity at home) may be useful to decrease severe hypertension and preterm birth (I-B; Low/Weak).
4. For women with preeclampsia who are hospitalized, strict bed rest is **not** recommended (I-D; Moderate/Weak).
5. For all other women with HDP, the evidence is insufficient to make a recommendation about the usefulness of some bed rest, which may nevertheless, be advised based on practical considerations (III-C; Low/Weak).

#### Comments

We lack RCT evidence examining the impact of the following on HDP outcomes: new severe dietary salt restriction for women with any HDP, new or ongoing salt restriction among women with pre-existing hypertension, heart healthy diet, calorie restriction among overweight women, or the impact of exercise. Preeclampsia is listed as a contraindication to vigorous exercise in the relevant SOGC 2003 Clinical Practice Guidelines [294].

No RCT data support workload reduction/cessation or stress management (e.g. meditation) for any of the HDPs when they are non-severe and outpatient-managed.

Outside pregnancy, stress management by relaxation techniques may improve BP control [7].

Bed rest is standard for women with a HDP [295,296]. Definitions have varied widely, compliance questioned [279], and RCT data are limited. For preeclampsia, strict (vs. some) bed rest in hospital does not alter outcomes [297]. For gestational hypertension, some bed rest in hospital (vs. routine activity at home) decreases severe hypertension (RR 0.58; 95% CI 0.38–0.89) and preterm birth (RR 0.53; 95% CI 0.29–0.99), although women prefer unrestricted activity at home [296]; whether benefits are from bed rest or hospitalization is not clear. In the absence of clear benefit, bed rest cannot be recommended due to potential harmful physical, psychosocial, and financial effects [298,299].

We found no cost effectiveness studies of dietary and lifestyle changes for HDP management.

The following recommendations apply to women with either pre-existing or gestational hypertension.

#### Place of care

#### Recommendations

1. In-patient care should be provided for women with severe hypertension or severe preeclampsia (II-2B; Low/Strong).
2. A component of care through hospital day units (I-B; Moderate/Strong) or home care (II-2B; Low/Strong) can be considered for women with non-severe preeclampsia or non-severe (pre-existing or gestational) hypertension.

#### Comments

Out-of-hospital care for preeclampsia assumes that full maternal and fetal assessments have been made and severe disease excluded (see *Classification of HDP*). Options include obstetrical day units and home care. Eligibility depends on home-to-facility distance, adequate maternal and fetal surveillance, patient compliance, non-labile BP, and absence of comorbid conditions or disease progression.

*Hospital day units.* Eligibility has varied from 30 to 60% of women assessed [300,301]. Hospital admission and days in hospital are reduced by day unit care, but outcomes and costs are similar [301–304]. Women prefer out-of-hospital care.

*Home care.* Eligibility is  $\leq 25\%$  [305]. Eligibility criteria vary widely but include accurate BP self-measurement (HBPM) [306], and consistency between home and hospital BP [307].

In observational studies, home care has been variably defined in terms of activity levels, self- vs. nurse/midwife assessments, and means of communication; [308,309] all involved daily contact and a (usually) weekly outpatient visit [305,308,309].

No RCTs have compared antepartum home care with either hospital day or inpatient care. For gestational hypertension, routine activity at home (vs. some bed rest in hospital) is associated with more severe hypertension (RR 1.72; 95% CI 1.12–2.63) and preterm birth (RR 1.89;

95% CI 1.01–3.45); women prefer routine activity at home [310,311].

In observational studies of antepartum home care (vs. inpatient care), hospital admission (25%) [309], re-admission (44%) [305] and maternal satisfaction rates [312] were high, with similar outcomes for either gestational hypertension [313], or mild preeclampsia [305]. Costs were lower with home care [309].

#### Antihypertensive therapy

For severe hypertension (BP of  $\geq 160$  mmHg systolic or  $\geq 110$  mmHg diastolic)

#### Recommendations

1. BP should be lowered to  $<160$  mmHg systolic and  $<110$  mmHg diastolic (I-A; Low/Strong).
2. Initial antihypertensive therapy in the hospital setting should be with nifedipine short-acting (capsules) (I-A; High/Strong), parenteral hydralazine (I-A; High/Strong), or parenteral labetalol (I-A; High/Strong).
3. Alternative antihypertensive medications include a nitroglycerin infusion (I-B; Moderate/Weak), oral methyldopa (I-B; Very low/Weak), oral labetalol (I-B; Moderate/Weak), oral clonidine (III-B; Low/Weak), or only postpartum, oral captopril (III-B; Very low/Weak).
4. Refractory hypertension may be treated with sodium nitroprusside (III-B; Low/Weak).
5. Nifedipine and  $MgSO_4$  can be used contemporaneously (II-2B; Moderate/Weak)
6.  $MgSO_4$  is not recommended solely as an antihypertensive agent. (I-E; High/Strong)
7. Continuous FHR monitoring is advised until BP is stable (III-I; Very low/Weak).

#### Comments

BP  $\geq 160/110$  mmHg should be confirmed after 15 min. Most women will have preeclampsia, and were normtensive recently. These hypertensive events are 'urgencies' even without symptoms.

In the 2011 World Health Organization (WHO) preeclampsia/eclampsia recommendations, antihypertensive treatment of severe hypertension was *strongly* recommended to decrease maternal morbidity and mortality [100]. Severe systolic hypertension is an independent risk factor for stroke in pregnancy [25]. Short-acting antihypertensives successfully lower maternal BP in  $\geq 80\%$  of women in RCTs of one antihypertensive vs. another (see below). Finally, the UK 'Confidential Enquiries into Maternal Deaths' identified failure to treat the severe (particularly systolic) hypertension of preeclampsia as the single most serious failing in the clinical care of women who died [2,314].

A hypertensive 'emergency' is associated with end-organ complications (e.g., eclampsia). Extrapolating from outside pregnancy, hypertensive emergencies require parenteral therapy (and arterial line) aimed at lowering mean arterial BP by no more than 25% over minutes to hours, and then further lowering BP to 160/100 mmHg over hours. Hypertensive 'urgencies' are without end-organ

complications and may be treated with oral agents with peak drug effects in 1–2 h (e.g., labetalol). Gastric emptying may be delayed or unreliable during active labour.

Recommendations have been restricted to antihypertensive therapy widely available in Canada. Most RCTs have compared parenteral hydralazine, parenteral labetalol, or calcium channel blockers (usually oral nifedipine). All are reasonable (doses in Table 6), with selection guided by associated medical conditions (e.g., asthma) or therapies (e.g., current full dose labetalol). One agent suffices in at least 80% of women.

Parenteral hydralazine, compared with any other short-acting antihypertensive, is associated with more adverse effects, including maternal hypotension, Caesarean delivery, and adverse FHR effects [315]. Compared with calcium channel blockers, hydralazine may be a *less* effective antihypertensive and associated with more maternal side effects [315–318]. Compared with parenteral labetalol, hydralazine may be a *more* effective antihypertensive but associated with more maternal hypotension and maternal side effects [315,319,320]; however, labetalol is associated with more neonatal bradycardia that may require intervention [315,319,321].

Compared with oral nifedipine or parenteral nicardipine, parenteral labetalol appears to be similarly effective for BP control [322–324].

Oral labetalol (200 mg) has been used with good effect within a regional pre-eclampsia protocol [325]. In a clinical trial of preterm severe hypertension, 100 mg of oral labetalol every 6 h achieved the stated BP goal (of about 140/90 mmHg) in 47% of women [326]. These data appear insufficient to support the UK recommendation to use oral labetalol as *initial* therapy for severe pregnancy hypertension [99]; however, if severe hypertension is detected in the office setting, an oral antihypertensive may be useful during transport to hospital for further evaluation and treatment.

The nifedipine preparations appropriate for treatment of severe hypertension are the capsule (bitten or swallowed whole) and the PA tablet [327] which is not currently available in Canada. The 5 mg (vs. 10 mg) capsule may reduce the risk of a precipitous fall in BP [328]. The risk of neuromuscular blockade (reversed with calcium gluconate) with contemporaneous use of nifedipine and  $MgSO_4$  is <1% [329,330].

$MgSO_4$  is not an antihypertensive, having the potential to lower BP transiently 30 min after a loading dose [331–334].

Infused nitroglycerin (vs. oral nifedipine) is comparably effective without adverse effects [335–337]. Mini-dose diazoxide (i.e., 15 mg IV every 3 min, vs. parenteral hydralazine) is associated with less persistent severe hypertension [338].

For refractory hypertension in intensive care, higher dose diazoxide can be considered (although there is more hypotension than with labetalol) [339] as can sodium nitroprusside (being mindful of the unproven risk of fetal cyanide toxicity) [340].

Postpartum, hydralazine, labetalol, nifedipine, and methyldopa are appropriate for treatment of severe hypertension and during breastfeeding [341,342]. Oral captopril

is effective outside pregnancy [343] and is acceptable during breastfeeding (<http://toxnet.nlm.nih.gov/>). Nitroglycerin, sodium nitroprusside and diazoxide have not been studied in breastfeeding. Oral clonidine has resulted in high serum levels in breastfed infants (<http://toxnet.nlm.nih.gov/>).

*For non-severe hypertension (BP of 140–159/90–109 mmHg) without comorbid conditions*

#### Recommendations

1. Antihypertensive drug therapy may be used to keep sBP at 130–155 mmHg and dBP at 80–105 mmHg (I-B; Low/Weak).
2. The choice of antihypertensive agent for initial treatment should be based on characteristics of the patient, contraindications to a particular drug, and physician and patient preference (III-C; Very low/Weak).
3. Initial therapy in pregnancy can be with one of a variety of antihypertensive agents available in Canada: methyldopa (I-A; High/Strong), labetalol (I-A; High/Strong), other beta-blockers (acebutolol, metoprolol, pindolol, and propranolol) (I-B; Moderate/Strong), and calcium channel blockers (nifedipine) (I-A; High/Strong),
4. Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) should not be used during pregnancy (II-2E; Moderate/Strong).
5. Atenolol and prazosin are not recommended prior to delivery (I-D; Moderate/Weak).

*For non-severe hypertension (BP of 140–159/90–109 mmHg) with comorbid conditions*

#### Recommendations

1. For women with comorbid conditions, antihypertensive drug therapy should be used to keep sBP at <140 mmHg and dBP at <90 mmHg (III-C; Low/Weak).
2. Initial therapy in pregnancy can be with one of a variety of antihypertensive agents as listed for women without co-morbidities (III-C; Very low/Weak).
3. Captopril, enalapril, or quinapril may be used postpartum, even during breastfeeding (III-B; Low/Weak).

#### Comments

Management of non-severe pregnancy hypertension is much debated. Any antihypertensive therapy will, compared with placebo or no therapy: decrease transient severe hypertension (RR 0.50; 95% CI 0.41–0.61) without a difference in other outcomes, including preeclampsia or preterm delivery [243]. However, antihypertensive lowering of BP may reduce fetal growth velocity [61,247,248]; not all subsequently published data are consistent with this [344]. The definitive CHIPS (Control of Hypertension In Pregnancy Study) RCT addressing the issue of BP targets in non-severe hypertension will publish its results in 2014 [345]. No reliable long-term developmental outcome data exist [346,347] (see *Effect on long-term child development*).

**Women without comorbid conditions** should receive antihypertensives to lower dBP to 80–105 mmHg,

**Table 6**The most commonly used agents for treatment of a BP  $\geq$  160/110 mmHg.

Agent	Dosage	Onset	Peak	Duration	Comments
Labetalol	Start with 20 mg IV; repeat 20–80 mg IV q 30 min, or 1–2 mg/min, max 300 mg (then switch to oral)	5 min	30 min	4 h	Best avoided in women with asthma or heart failure. Neonatology should be informed if the woman is in labour, as parenteral labetalol may cause neonatal bradycardia
Nifedipine	5–10 mg capsule to be swallowed, or bitten then swallowed, every 30 min	5–10 min	30 min	~6 h	Staff should be aware of the distinction between short-acting nifedipine capsules used for treatment of severe hypertension, and both the intermediate-acting PA tablets (that can be used for treatment of non-severe or severe hypertension), and the slow-release tablets [XL] that are used for non-severe hypertension
Hydralazine	Start with 5 mg IV; repeat 5–10 mg IV every 30 min, or 0.5–10 mg/hr IV, to a maximum of 20 mg IV (or 30 mg IM)	5 min	30 min		May increase the risk of maternal hypotension

recognizing that non-severe hypertension is not an absolute indication for treatment outside pregnancy [7]. The upper dBp acknowledges BP variability, BP measurement inaccuracies, and the desire to avoid a dBp  $\geq$  110 mmHg. The lower dBp reflects concern around limiting uteroplacental perfusion [247,248], and recommendations outside pregnancy [7].

In contrast, **women with comorbid conditions** (Table 1) should probably have their BP lowered to <140/90 mmHg. Lower limits for BP goals are unclear. Outside pregnancy, <130/80 mmHg is specified only with diabetes mellitus but to achieve risk reduction over a longer time-frame [7,348].

CHEP recommendations provide initial guidance about treatment of secondary causes of hypertension [7].

There is little to guide the choice of antihypertensives in women with or without co-morbidities. Many antihypertensives have been compared with placebo or no therapy: methyldopa, labetalol, other pure beta-blockers (acebutolol, mepindolol, metoprolol, pindolol, and propranolol), calcium channel blockers (isradipine, nifedipine, and verapamil), hydralazine, prazosin, and ketanserin [246]; ketanserin, isradipine, nifedipine, and mepindolol are not used in Canada.

In comparative trials (usually of beta-blockers vs. methyldopa), beta-blockers (i.e., labetalol, pindolol, metoprolol, or oxprenolol) were more effective antihypertensives than methyldopa (RR 0.75; 95% CI 0.58–0.94), without other differences in outcomes [246,347] (see 'Aspects of care specific to women with pre-existing hypertension' and 'Effects on long-term child development').

Be familiar with a number of antihypertensive options. Only 30–50% of non-pregnant patients will respond to a given antihypertensive, and monotherapy will be insufficient if BP is more than 20/10 mmHg above target. Women may have a contraindication to a specific medication (e.g., severe asthma and beta-blockers) or a characteristic that makes an agent preferable (e.g., Black race and calcium channel blockers).

There is no renoprotection agent that can replace ACE inhibitors or ARBs for women with diabetes mellitus and pre-pregnancy microalbuminuria; however, BP control is both a critical element of ACE inhibitor renoprotection

and can be provided by other antihypertensives. Some ACE inhibitors are acceptable during breastfeeding (see 'Severe Hypertension').

Labetalol and methyldopa are the oral agents used most frequently in Canada [350] (Table 7). ACE inhibitors and ARBs are fetotoxic [351] (particularly nephrotoxic) [352]. Prazosin may cause stillbirths [353]. Atenolol (in contrast with other cardioselective beta-blockers) may be associated with reduced fetal growth velocity [354–358], making other agents preferable. Oral hydralazine monotherapy is not recommended due to maternal side effects [359]. Thiazide diuretics can be used [238]. Oral antihypertensives do not appear to change FHR or pattern; relevant changes are best attributed to evolution of the underlying HDP, not to the antihypertensive agent.

The cost-effectiveness of antihypertensives for severe or non-severe hypertension is unknown.

#### Corticosteroids for acceleration of fetal pulmonary maturity

##### Recommendations

1. Antenatal corticosteroid therapy should be considered for all women who present with preeclampsia at  $\leq 34^6$  weeks gestation (I-A; High/Strong).
2. Antenatal corticosteroid therapy should be considered for women who present at  $\leq 34^6$  weeks with gestational hypertension (despite the absence of proteinuria or 'adverse conditions') only if delivery is contemplated within the next 7 days (III-L; Low/Weak).
3. A rescue dose of corticosteroids may be considered for women at  $\leq 34^6$  weeks who remain at high risk of pre-term delivery 7 days or more after an initial course of antenatal corticosteroids (I-C; Low/Weak).
4. Antenatal corticosteroids may be considered for women delivered by elective Caesarean delivery at  $\leq 38^6$  weeks' gestation to reduce respiratory morbidity (I-B; Low/Weak).

##### Comments

When administered at  $\leq 34^6$  weeks, antenatal corticosteroids accelerate fetal pulmonary maturity and decrease neonatal mortality and morbidity, including women with

**Table 7**

Doses of the most commonly used agents for treatment of a BP of 140–159/90–109 mmHg.

Agent	Dosage	Comments
Methyldopa	250–500 mg po bid-qid (max 2 g/d)	There is no evidence to support a loading dose of methyldopa
Labetalol	100–400 mg po bid-tid (max 1200 mg/d)	Some experts recommend a starting dose of 200 mg po bid
Nifedipine	XL preparation (20–60 mg po OD, max 120 mg/d)	Ensure that the correct form of nifedipine has been prescribed so that the XL preparation is not confused with the capsules

HDPs [360]. RCTs that administered steroids at 33<sup>0</sup> to 34<sup>6</sup> weeks resulted in reduced neonatal RDS [360], a subject of ongoing trials. The beneficial effects of steroids can be observed when the first dose is administered as late as within 4 h before birth. There is no evidence of short- or long-term maternal or fetal adverse effects of a single course of antenatal corticosteroids.

If expectantly managed, women with preeclampsia remote from term (usually <34<sup>0</sup> weeks) will be delivered within two weeks of corticosteroid administration, but the duration of pregnancy prolongation varies from hours to weeks. All eligible women with preeclampsia should receive antenatal corticosteroids.

If women with preeclampsia remain pregnant seven or more days after receipt of antenatal corticosteroids, there is insufficient information available to recommend another course. Repeated dose antenatal corticosteroids are associated with short-term neonatal respiratory, without demonstrated long-term, benefits [361] and some concern about harm [362].

One third of women with gestational hypertension at <34<sup>0</sup> weeks will develop preeclampsia over an average of 5 weeks; delivery is unlikely within 7 days [65]. Clinicians should administer corticosteroids to those women whom they feel are at high risk of delivery within a week.

Antenatal corticosteroids may cause significant, transient changes in FHR and variability up to 4 days after administration [363–365].

Prior to elective Caesarean delivery at ≤38<sup>6</sup> weeks, antenatal corticosteroids decrease the excess neonatal respiratory morbidity and NICU admissions [366,367]. All subgroup analyses have not necessarily revealed such benefits following Caesarean or vaginal delivery [360].

No cost effectiveness data were identified for hypertensive pregnant women.

#### Timing of delivery

#### Recommendations

Delivery is the only intervention that initiates resolution of preeclampsia, and women with gestational hypertension or pre-existing hypertension may develop preeclampsia.

#### Women with pre-eclampsia

1. Consultation with an obstetrician (by telephone if necessary) is mandatory in women with severe preeclampsia (III-B; Low/Strong).
2. All women with severe preeclampsia should be delivered immediately (either vaginally or by Caesarean), regardless of gestational age (III-C; Low/Strong).

3. For women with non-severe preeclampsia at <24<sup>0</sup> weeks' gestation, counselling should include as an option, information about delivery within days (II-2B; Low/Weak).
4. For women with non-severe preeclampsia at 24<sup>0</sup>–36<sup>6</sup> weeks' gestation, expectant management should be considered, but only in perinatal centres capable of caring for very preterm infants (I-B; Moderate/Weak).
5. For women with non-severe preeclampsia at 34<sup>0</sup>–36<sup>6</sup> weeks' gestation, there is insufficient evidence to make a recommendation about the benefits or risks of expectant management (III-L; Low/Weak).
6. For women with preeclampsia at ≥37<sup>0</sup> weeks' gestation, immediate delivery is recommended (I-A; High/Strong).
7. For women with non-severe preeclampsia complicated by HELLP syndrome at 24<sup>0</sup>–34<sup>6</sup> weeks' gestation, consider delaying delivery long enough to administer antenatal corticosteroids for acceleration of fetal pulmonary maturity if there is temporary improvement in maternal laboratory testing (II-2B; Low/Weak).
8. All women with HELLP syndrome at ≥35<sup>0</sup> weeks' gestation should be considered for immediate delivery (II-2B; Moderate/Strong).

#### Women with gestational hypertension

1. For women with gestational hypertension (without preeclampsia) at ≥37<sup>0</sup> weeks' gestation, delivery within days should be discussed (I-B; Low/Weak).
2. For women with gestational hypertension (without preeclampsia) at <37<sup>0</sup> weeks' gestation, there is insufficient evidence to make a recommendation about the benefits or risks of expectant management (III-L; Very low/Weak).

#### Women with pre-existing hypertension

1. For women with uncomplicated pre-existing hypertension who are otherwise well at ≥37<sup>0</sup> weeks' gestation, delivery should be considered at 38<sup>0</sup>–39<sup>6</sup> weeks' gestation (II-1B; Low/Weak).

#### Comments

**Preeclampsia.** The Confidential Enquiries into Maternal Death have related underappreciation of risk in preeclampsia to potentially avoidable complications. Subspecialty consultation has been advised, by telephone if necessary, particularly for women with severe preeclampsia [314].

The phrase, “planned delivery on the best day in the best way,” reflects the myriad of considerations regarding timing (and mode) of delivery [325]. Timing delivery will reflect evolving adverse conditions (Table 2). Consensus-derived indications for delivery are: (i) term gestation, (ii) development of severe maternal HDP-associated

complication(s) (Table 2) [92], (iii) stillbirth, or (iv) results of fetal monitoring that indicate delivery according to general obstetric practice [92,363,368]. Currently, no tool exists to guide balancing risks, benefits, and the preferences of the woman and her family.

The best treatment for the mother is always delivery, limiting her exposure to preeclampsia, so expectant management is best considered when potential perinatal benefits are substantial, usually at early gestational ages.

Expectant management of preeclampsia refers to attempted pregnancy prolongation following a period of maternal and fetal observation and assessment, and maternal stabilization. Following this, 40% will be considered eligible for pregnancy prolongation [92]. Expectant management should occur only in an experienced unit where neonates can be cared for at the woman's current gestational age (as delivery cannot be accurately anticipated).

Expectant management at <24<sup>0</sup> weeks is associated with perinatal mortality >80% and maternal complications of 27–71% (including one maternal death) [368,369]. Termination of pregnancy should be discussed.

Expectant management at 24<sup>0</sup>–33<sup>6</sup> weeks may decrease neonatal respiratory distress syndrome, necrotizing enterocolitis, and NICU care, despite poor fetal growth velocity during the time gained [370,371]. Rates of serious maternal complications appear very low (median <5%) [92]. Timing of delivery should be individualized, recognizing that on average, pregnancy prolongation is 2 weeks. If preeclampsia is complicated by HELLP, fewer days will be gained (median 5) and serious maternal morbidity will be higher (median 15%); >50% have temporary improvement of HELLP which may enable regional anaesthesia or vaginal delivery [92].

For late preterm preeclampsia (34<sup>0</sup>–36<sup>6</sup> weeks), delaying delivery may facilitate cervical ripening and vaginal delivery [372], but substantial perinatal benefits are not anticipated and there are concerns about the vulnerability of the fetal brain to injury at this time [373]. We await data from two RCTs (HYPITAT-II, [www.studies-obsgyn.nl](http://www.studies-obsgyn.nl); ClinicalTrials.gov NCT00789919). In antihypertensive comparison RCTs near or at term, pregnancy prolongation was associated with a Caesarean delivery rate of ~70% [374–378], with little or no information about pregnancy prolongation or other maternal or perinatal outcomes.

With term preeclampsia (37<sup>0</sup>–42<sup>0</sup> weeks) labour induction is indicated to reduce poor maternal outcome (RR 0.61, 95% CI 0.45–0.82) [379]. This policy has a favourable impact on health-related quality of life [380].

**Gestational hypertension.** Women with term gestational hypertension probably benefit from labour induction by decreasing poor maternal outcome (RR 0.71, 95% CI 0.59, 0.86, preeclampsia and gestational hypertension data combined) [379].

**Preexisting hypertension.** Among women with uncomplicated pre-existing hypertension, delivery at 38<sup>0</sup>–39<sup>6</sup> weeks appears to optimize the trade-off between the risk of adverse fetal (stillbirth) or maternal complications (superimposed preeclampsia and abruption) that increase with gestational age, and neonatal mortality and morbidity that

decreases in incidence with gestational age [381]. Trial data are needed.

We were unable to identify data on the cost-effectiveness of labour induction for women with a HDP before 34<sup>0</sup> weeks. For women with gestational hypertension or preeclampsia near term (34<sup>0</sup>–36<sup>6</sup> weeks), a policy of labour induction is cost-effective based on neonatal and maternal morbidity, based on controlled retrospective data; labour induction cost CAD\$299 more but was associated with better quality of life [[www.nice.org.uk/guidance](http://www.nice.org.uk/guidance)] [382]. For women with gestational hypertension or preeclampsia at ≥37<sup>0</sup> weeks, labour induction is cost-saving (by CAD\$1,065) due to less antepartum resource use [383].

### Mode of delivery

#### Recommendations

1. For women with any HDP, vaginal delivery should be considered unless a Caesarean delivery is required for the usual obstetric indications (II-2B; Low/Strong).
2. If vaginal delivery is planned and the cervix is unfavourable, then cervical ripening should be used to increase the chance of a successful vaginal delivery (1-A; Moderate/Strong).
3. At a gestational age remote from term, women with HDP with evidence of fetal compromise may benefit from delivery by emergent Caesarean delivery (II-2B; Low/Strong).
4. Antihypertensive treatment should be continued throughout labour and delivery to maintain sBP at <160 mmHg and dBp at <110 mmHg (II-2B; Low/Strong).
5. The third stage of labour should be actively managed with oxytocin 5 units IV or 10 units IM, particularly in the presence of thrombocytopenia or coagulopathy (I-A; Moderate/Strong).
6. Ergometrine maleate should not be administered to women with any HDP, particularly preeclampsia or gestational hypertension; alternative oxytocics should be considered (II-3D; Low/Strong).

#### Comments

All women with a HDP should be considered for labour induction. Choosing the mode of delivery should consider both the gestational age and fetal status. In severe early-onset preeclampsia with clinical evidence of fetal compromise, Caesarean may be preferable.

For labour induction, cervical ripening (even with an unfavourable cervix), increases the chance of vaginal delivery [384,385]. With severe preeclampsia, this will take more time and be less successful compared with normotensive pregnancy [386,387]. Neither IUGR nor oligohydramnios are contraindications to induction [388].

Rates of vaginal delivery after induction are 6.7–10% at 24–28 weeks (suggesting advisability of Caesarean with viable fetuses), 47.5% at 28–32 weeks, 68.8% at 32–34 weeks, and 30% with birthweights <1500 g [385,388–391]. Vaginal delivery likelihood is reduced (but still exceeds 50%) when there is increased umbilical artery resistance [392,393]. The following predict Caesarean delivery: absent or reversed umbilical artery end-diastolic flow,

abnormal BPP, and abnormal sequential changes in Doppler studies of the fetal circulation [394–397].

Preeclampsia is associated with thrombocytopenia and coagulopathy, and active management of the third stage [398], avoiding ergometrine (ergonovine maleate), should be performed to avoid postpartum haemorrhage [399–404].

*Anaesthesia, including fluid administration and coagulation concerns in neuraxial techniques*

#### Recommendations – General principles

1. The anaesthesiologist should be informed when a woman with preeclampsia is admitted to the delivery suite (II-3B; Low/Strong).
2. Early insertion of an epidural catheter (in the absence of contraindications) is recommended for control of labour pain (I-A; Moderate-Strong/Strong).
3. In the absence of contraindications, all of the following are acceptable methods of anaesthesia for women undergoing Caesarean delivery: epidural, spinal, combined spinal-epidural, and general anaesthesia (I-A; Moderate-Strong/Strong).
4. A routine fixed intravenous fluid bolus should not be administered prior to neuraxial anaesthesia (I-E; Low/Strong).

#### Recommendations – Fluid administration

5. Intravenous and oral fluid intake should be minimized in women with preeclampsia, to avoid pulmonary oedema (II-2B; Low/Strong).

6. Fluid should not be **routinely** administered to treat oliguria (<15 mL/h for 6 consecutive hours) (III-D; Very low/Weak).
7. For treatment of persistent oliguria, neither dopamine nor furosemide is recommended (I-E; Moderate/Strong).
8. Phenylephrine or ephedrine may be used to prevent or treat hypotension during neuraxial anaesthesia (I-A; Moderate/Strong).

#### Recommendations – Monitoring

9. Arterial line insertion may be used for continuous arterial BP monitoring when BP control is difficult or there is severe bleeding (II-3B; Very low/Strong).
10. Central venous pressure monitoring is not routinely recommended, and if a central venous catheter is inserted, it should be used to monitor trends and not absolute values (II-2D; Very low-low/Strong).
11. Pulmonary artery catheterization is not recommended unless there is a specific associated indication (III-D; Very low/Strong), and then, only in an intensive care unit setting (III-B; Very low/Strong).

#### Recommendations – Coagulation

12. Upon admission to delivery suite, women with preeclampsia should have a platelet count done (II-1A; Low/Strong).
13. Neuraxial analgesia and/or anaesthesia are appropriate in women:
  - a. With preeclampsia, provided there are no associated coagulation concerns (see Table 8) (II-2E; Very low/Weak);

**Table 8**  
Eligibility for neuraxial anaesthesia.\*

Treatment with ASA or heparin	Normal platelet count	Low platelet count & Normal INR and aPTT	Abnormal INR or aPTT (regardless of platelet count) <sup>ε</sup>
<b>None or Low dose ASA</b>	✓	✓ – if platelet count > 75×10 <sup>9</sup> /L Unclear – if platelet count 50–75×10 <sup>9</sup> /L X – if platelet count < 50×10 <sup>9</sup> /L	✗ Contraindicated
UFH <10,000 IU/d (SC)	✓	Unclear	
>10,000 IU/d (SC)	0–4 h after last dose ✓ 4 h after last dose and a normal aPTT ✓	Unclear	
Therapeutic dose (iv)	4 h after last dose and a normal aPTT ✓	Unclear	
LMWH Prophylactic dose	✓ 10–12 h after last dose	Unclear	
Therapeutic dose	24 h after last dose ✓	Unclear	
<b>Low dose ASA + prophylactic UFH or LMWH<sup>  </sup></b>	Unclear <sup>f</sup>	Unclear	

ASA, aspirin; LMWH, low molecular weight heparin; SC, subcutaneous; UFH, unfractionated heparin).

\* These recommendations are based on the absence of a rapidly falling platelet count or KNOWN platelet dysfunction (e.g., von Willebrand's disease).

<sup>ε</sup> Other than a lupus anticoagulant.

<sup>||</sup> Prophylactic doses of unfractionated heparin are defined as ≤10,000 IU/d.

<sup>f</sup> Unless ASA is stopped 7 days or more before delivery.

- b. With a platelet count  $>75 \times 10^9/L$  (II-2B; Moderate-high/Strong);
- c. Taking low-dose ASA in the presence of an adequate platelet count (I-A; Very low/Weak);
- d. Receiving unfractionated heparin (UFH) in a dose of  $\leq 10,000$  IU/d subcutaneously, 4 h after the last dose and possibly immediately after the last dose without any delay (III-B; Very low/Weak);
- e. Receiving UFH in a dose  $>10,000$  IU/d subcutaneously, if they have a normal aPTT 4 h after the last dose (III-B; Very low/Weak);
- f. Receiving intravenous heparin in a therapeutic dose if they have a normal aPTT 4 h after the last dose (III-B; Very low/Weak); or
- g. Receiving low-molecular weight heparin (LMWH) a minimum of 10–12 h after a prophylactic dose, or 24 h after a therapeutic dose (III-B; Very low/Weak).

### General principles

Communication between caregivers is essential [2]. Early consultation (by telephone if necessary) with anaesthesia should occur, at the latest with delivery suite admission of a woman with preeclampsia. Anaesthesiologists may co-manage hypertension, maternal end-organ dysfunction, and use of medications with anaesthesia/analgesia implications.

Early placement of an epidural catheter is advantageous to: (i) attenuate labour pain-induced increases in cardiac output and BP [405–407], and in the event that either (ii) thrombocytopenia develops or (iii) Caesarean delivery is required. Neither epidural nor combined spinal-epidural, analgesia harms the fetus [405,408,409] or increases Caesarean delivery in severe preeclampsia [410,411].

If neuraxial analgesia and/or anaesthesia is contraindicated, intravenous opioid analgesia is a reasonable alternative; but neonatal depression may result and require naloxone [412].

For Caesarean delivery, spinal is preferred over epidural anaesthesia (unless already placed) because of its more rapid onset and smaller calibre needle [413]. If time permits, spinal is preferred over general anaesthesia to avoid the hypertensive response to intubation (attenuated by anti-hypertensives or opioids); spinal is, however, associated with lower cord pH and higher cord base deficit of uncertain clinical significance [414–419]. Spinals do not alter uteroplacental haemodynamics [420]. Difficult (or failed) intubation for general anaesthesia in women with HDPs is more common [421,422].

**Fluid administration.** Routine preloading with a fixed volume of crystalloid (i.e., 500–1000 mL) will not prevent BP falls in normal women prior to Caesarean delivery [423]; no specific studies exist for HDPs. Preloading may increase the risk of life-threatening pulmonary oedema [2]. Hypotension should be treated with vasopressors as an infusion or small boluses [424].

Oliguria ( $<15$  mL/h) is common in preeclampsia, particularly postpartum. In the absence of pre-existing renal

disease or a rising creatinine, oliguria should be tolerated over hours, to avoid volume-dependent pulmonary oedema [2,425,426]. Fluid balance should be closely monitored, and furosemide limited to pulmonary oedema treatment, as the benefits of furosemide (and dopamine) for oliguria are uncertain [427,428].

**Monitoring.** Early ( $<34$  weeks) and late ( $\geq 34$  weeks) onset preeclampsia may have different haemodynamics (i.e., low cardiac output (CO)/high systemic vascular resistance (SVR) for the former and high CO/low SVR for the latter) [429]. For resistant/labile hypertension, non-invasive or minimally invasive haemodynamic assessment, particularly transthoracic echocardiography, can be used to guide therapy; results correlate well with invasive monitoring [430].

Almost all women can be monitored effectively by vital signs and oxygen saturation. Central venous pressure (CVP) monitoring should be limited to haemodynamically unstable women. CVP monitoring can be used for trends (including response to therapy) rather than for diagnosis. Pulmonary artery catheterization should be limited to the ICU.

**Neuraxial analgesia/anaesthesia and coagulation.** Most guidance for neuraxial anaesthesia in women with preeclampsia and coagulation disorders comes from non-obstetric literature and guidelines based mainly on expert opinion.

All women with a HDP should have a platelet count, noting the number and trend in the count. Tests of platelet function are not indicated, as results do not correlate with bleeding in the spinal space [431].

Neuraxial haematoma (in the epidural, spinal, or subdural spaces) is rare ( $<1:150,000$  epidurals,  $<1:220,000$  spinals) [432]. However, the potential to cause permanent neurological dysfunction promotes concern in women either with low platelet counts or taking medication affecting coagulation [433]. These women should be assessed soon after the block has worn off to exclude back pain or new/progressive neurological complications [432].

#### ○ Thrombocytopenia

Neuraxial haematomas have not been reported with platelet counts above  $75 \times 10^9/L$ , in the absence of platelet dysfunction or associated coagulopathy [434]. Practice varies widely regarding an acceptable platelet count (range  $50\text{--}100 \times 10^9/L$ ) prior to neuraxial anaesthesia or catheter removal [413,435]

#### ○ Aspirin

Women on low-dose aspirin (60–81 mg) are eligible for neuraxial anaesthesia [436,437]. There is minimal evidence about the safety of neuraxial anaesthesia for women on higher doses of aspirin. Of 61 cases of neuraxial haematoma associated with non-obstetric neuraxial block, one was associated with higher dose aspirin therapy [438], while none of 674 patients who received preoperative aspirin (median dose 350 mg) developed a spinal haematoma [439,440]. More recent cases of neuraxial haematoma associated with 81 mg of aspirin were associated with concomitant heparin therapy [441].

Coagulation tests are indicated with thrombocytopenia, maternal end-organ dysfunction of preeclampsia, or clinical bleeding [80,87], with some anaesthesiologists testing routinely prior to neuraxial analgesia/anaesthesia [435,442].

#### ○ Heparin

Advice regarding anaesthetic management of the heparinized patient differs, based largely on expert opinion [433].

Following a prophylactic dose of unfractionated heparin (UFH) subcutaneously (maximum 10,000 IU/d), advice varies from no delay to a delay of 4 h [433,443]; 4 h is consistent with the known non-pregnancy UFH pharmacokinetics despite an earlier peak effect in pregnancy [444]. While generally unnecessary, aPTT can be checked prior to neuraxial analgesia/anaesthesia [433,445].

With therapeutic subcutaneous UFH, an aPTT  $\geq$  4 h after the last dose should be confirmed to be normal prior to initiating neuraxial analgesia/anaesthesia or removing a neuraxial catheter.

When to *initiate* prophylactic or therapeutic UFH after neuraxial block is at least one hour following either block placement or catheter removal [433,443,446].

Women on LMWH are ineligible for neuraxial anaesthesia until at least 10–12 h (prophylactic dose) or 24 h (therapeutic dose) after their last dose, based on non-pregnancy reports of neuraxial haematomas [443]. Some anaesthesiologists prefer to wait 24 h after any dose. Therefore, switching from prophylactic LMWH to UFH is common in late pregnancy [447].

If there were blood in the needle or epidural catheter when siting a neuraxial block, initiating LMWH should be delayed for 24 h [443], during which period early mobilization and non-pharmacological methods can be used in women at higher thromboembolic risk.

Indwelling neuraxial catheters can be maintained with prophylactic doses of UFH ( $\leq$ 10,000 IU/day) and single-daily prophylactic LMWH, without use of other haemostasis-altering agents.

#### ○ Aspirin and heparin

Based on non-obstetric data, women receiving aspirin and either prophylactic LMWH or UFH are at higher risk of neuraxial haematomas. Neuraxial anaesthesia should be avoided in patients on aspirin ( $>$ 75 mg daily) and LMWH [443], aspirin could be discontinued 2–3 days prior to neuraxial anaesthesia if preoperative heparin thromboprophylaxis is used [445,446].

### Aspects of care specific to women with pre-existing hypertension

#### Recommendations

1. Pre-conceptual counselling for women with pre-existing hypertension is recommended (III-C; Very low/Weak).
2. The following antihypertensive drugs are acceptable for use in the first trimester of pregnancy: methyldopa, labetalol, and nifedipine (all II-2B; all Low/Weak).
3. ACE inhibitors and ARBs should be discontinued when planning pregnancy or as soon as pregnancy is diagnosed (II-2D; Low/Weak).

4. Atenolol should be discontinued when pregnancy is diagnosed (I-D; Low/Weak).
5. Planned changes in antihypertensive agent(s) for care in pregnancy should be made while the woman is planning pregnancy if the woman has uncomplicated pre-existing hypertension, or, if in the presence of comorbid conditions, she is likely to conceive easily (within 12 months) (III-L; Very low/Weak).

#### Comments

The major issues to address are the teratogenicity of antihypertensives, continuing antihypertensives during pregnancy, and continuing pre-pregnancy cardiovascular risk reduction therapy (e.g., aspirin, statins).

Pre-conceptual counselling is ideal, but as 50% of pregnancies are unplanned, inadvertent antihypertensive exposures will occur. Contraception efficacy and the potential for teratogenicity must be considered when prescribing antihypertensives to reproductive age women, all of whom should take  $\geq$ 0.4 mg/day of folate prior to pregnancy.

As BP usually falls in pregnancy (nadir  $\approx$ 20 weeks), before rising towards pre-pregnancy levels by term, women with pre-existing hypertension may not need to continue antihypertensives from early pregnancy. Antihypertensive discontinuation does not alter preeclampsia risk [448] (see *Antihypertensive therapy*.)

Any potential teratogenicity must be assessed relative to the baseline risk of major malformations: 1–5% of pregnancies. Most antihypertensives have not been found to be teratogenic, but the quality of the information is only fair for most. The 2010 UK NICE guidelines describe thiazides as teratogenic (unsupported statement). ACE inhibitors may increase the risk of major (particularly cardiovascular or central nervous system) malformations [449]. [Teratogenicity information is readily available from the DART database [450] and Motherisk, [www.motherisk.org](http://www.motherisk.org).] The adverse effects of atenolol on fetal growth have been particularly associated with use from early pregnancy [354–358].

Whether or when to replace ACE inhibitors, angiotensin-receptor blockers (ARBs), atenolol, or less commonly used antihypertensives pre-pregnancy or when pregnancy is diagnosed, and if so, with what is uncertain, but the following should be considered:

*Is there an alternative agent available?* If ACE inhibitors and ARBs are being given for renoprotection, no *equivalent* agent is available for use in pregnancy; however, much of ACE/ARB-related renoprotection is provided lowering BP, achievable by alternatives [7].

*How long will conception take?* Normally, conception may take up to 12 months, but women over 30 years have a higher incidence of subfertility. If an ACE inhibitor is discontinued pre-pregnancy in a woman with renal disease, yet conception does not occur after 12 months and proteinuria is rising despite excellent BP control (i.e.,  $<$ 140/90 mmHg), it may be prudent to reinstate ACE inhibition, perform monthly pregnancy tests, and proceed with investigations of subfertility. A multidisciplinary approach towards comorbidities and/or cardiovascular risk factors is recommended.

Although existing data are reassuring about use of statins in pregnancy, they should be discontinued pre-pregnancy or as soon as pregnancy is diagnosed until further data are available. Information about safety with treatment at 24<sup>0</sup>–33<sup>6</sup> weeks will come from the StAmP Trial (ISRCTN 23410175).

For information on management of renal disease in pregnancy, see the update by Davison [451].

### Aspects of care for women with preeclampsia

#### Magnesium sulfate (MgSO<sub>4</sub>) for eclampsia (Prophylaxis or Treatment)

#### Recommendations

1. MgSO<sub>4</sub> is recommended for first-line treatment of eclampsia (I-A; High/Strong).
2. MgSO<sub>4</sub> is recommended as prophylaxis against eclampsia in women with severe preeclampsia (I-A; High/Strong).
3. MgSO<sub>4</sub> may be considered as prophylaxis against eclampsia in women with non-severe preeclampsia with severe hypertension, headaches/visual symptoms, right upper quadrant/epigastric pain, platelet count <100,000 × 10<sup>9</sup>/L, progressive renal insufficiency, and/or elevated liver enzymes, based on cost considerations (I-C; Moderate/Strong).
4. MgSO<sub>4</sub> should be used in standard dosing, usually 4 g IV loading dose followed by 1 g/h (I-A; Moderate/Strong).
5. Routine monitoring of serum Mg levels is not recommended (I-E; Low/Strong).
6. Phenytoin and benzodiazepines should not be used for eclampsia prophylaxis or treatment, unless there is a contraindication to MgSO<sub>4</sub> or it is ineffective (I-E; High/Strong).
7. In women with pre-existing or gestational hypertension, MgSO<sub>4</sub> should be considered for fetal neuroprotection in the setting of 'imminent preterm birth' (within the next 24 h) at ≤31<sup>6</sup> weeks (I-A; Moderate/Strong).
8. Delivery should not be delayed in order to administer antenatal MgSO<sub>4</sub> for fetal neuroprotection if there are maternal and/or fetal indications of emergency delivery (III-E; Very low/Strong).

#### Comments

For eclampsia, MgSO<sub>4</sub> more than halves recurrent seizure rates compared with phenytoin [452], diazepam [453], or a lytic cocktail [454]. Also, MgSO<sub>4</sub> (vs. diazepam) reduces maternal death; benzodiazepines should not be used for seizure termination. Loading is with MgSO<sub>4</sub> 4 g IV (or 5 g in South Africa) over 5 min, followed by infusion of 1 g/h. Treatment of any recurrent seizures is with another 2–4 g IV over 5 min. Serum Mg<sup>2+</sup> levels are unnecessary, with women followed clinically for adverse Mg<sup>2+</sup>-related effects.

In women with preeclampsia, MgSO<sub>4</sub> (vs. placebo or no therapy) more than halves eclampsia occurrence (RR 0.41; 95% CI 0.29–0.58) [455,456]. Loading is with MgSO<sub>4</sub> 4 g IV over 10–15 min, followed by infusion of 1 g/h. The NNT (95% CI) to prevent one seizure is 50 (34–100) with severe

preeclampsia and 100 (100–500) with non-severe preeclampsia. MgSO<sub>4</sub> decreases abruption risk (RR 0.64; 95% CI 0.50–0.83; NNT 100 [50–1000]) but increases Caesarean delivery (RR 1.05; 95% CI 1.01–1.10) and side effects (RR 5.26; 95% CI 4.59–6.03). MgSO<sub>4</sub> (vs. phenytoin) reduces eclampsia (RR 0.08; 95% CI 0.01–0.60) but increases Caesarean delivery (RR 1.21; 95% CI 1.05–1.41) [455]. MgSO<sub>4</sub> (vs. nimodipine) reduces eclampsia, but there were more respiratory problems (RR 3.61; 95% CI 1.01–12.91) and the need for additional antihypertensives (RR 1.19; 95% CI 1.08–1.31) [455].

In preeclampsia, although the risk of eclampsia is lower with MgSO<sub>4</sub> (vs. placebo, no therapy, or other anti-convulsants), it is controversial whether women with non-severe preeclampsia should receive MgSO<sub>4</sub>, due to Caesarean delivery and maternal adverse effect risks, as well as cost (i.e., US\$23000 to prevent one seizure if administered to all women with preeclampsia) [457]. There is no international consensus on what defines severe pre-eclampsia. This document defines it as pre-eclampsia requiring delivery, due to serious maternal end-organ involvement and/or fetal compromise (see *Classification*). For eclampsia prevention in the setting of non-severe pre-eclampsia, we have added to the indication for MgSO<sub>4</sub> (in recommendation 3 above), the following symptoms/signs as these are included in the definition of severe pre-eclampsia by other organizations: severe hypertension, headaches/visual symptoms, right upper quadrant/epigastric pain, platelet count <100,000 × 10<sup>9</sup>/L, progressive renal insufficiency, and/or elevated liver enzymes. However, it should be noted that moving from universal prophylaxis to selection of only those women with more severe disease may increase (marginally) eclampsia and associated general anaesthesia and adverse neonatal outcomes [458].

The role of modified MgSO<sub>4</sub> protocols is uncertain (i.e., eclampsia treatment with loading dose-only or low-dose regimens, and eclampsia prevention with abbreviated postpartum courses vs. 24 h of treatment) [459–463].

MgSO<sub>4</sub> is recommended for fetal neuroprotection in the setting of imminent preterm birth (within the next 24 h) at ≤31<sup>6</sup> weeks, and could be considered at up to 33<sup>6</sup> weeks [464].

For MgSO<sub>4</sub> *treatment* of eclampsia, we were unable to identify a cost-effectiveness analysis. For women with pre-eclampsia, MgSO<sub>4</sub> prevents eclampsia but costs more (vs. no treatment) [457]. In high income countries, the NNT to prevent one case of eclampsia is 43 [68], with an incremental cost of US\$21,202; this would be \$12,942 if treatment were restricted to severe preeclampsia. Conventionally, \$50,000 per case prevented is the threshold for 'willingness to pay'. MgSO<sub>4</sub> for fetal neuroprotection (vs. no treatment) is highly cost-effective [465].

#### Plasma volume expansion for preeclampsia

#### Recommendation

1. Plasma volume expansion is not recommended for women with preeclampsia (I-E; Moderate/Strong).

### Comments

Women with preeclampsia are intravascularly volume contracted with high sympathetic tone. Colloid solutions do not improve maternal, perinatal or 12 month neurodevelopmental outcomes, but may increase Caesarean deliveries, decrease pregnancy prolongation, and increase pulmonary oedema [466,467].

### Therapies for HELLP syndrome

#### Recommendations

1. Every obstetrical centre should be aware of the local delay between ordering and receiving platelets units (IIIB; Very low/Strong).
2. For a platelet count  $<20 \times 10^9/L$  with HELLP, platelet transfusion is recommended, regardless of mode of delivery (IIIB; Low/Strong).
3. For a platelet count  $20-49 \times 10^9/L$  with HELLP, platelet transfusion is recommended prior to Caesarean delivery (IIIB; Low/Strong).
4. For a platelet count  $20-49 \times 10^9/L$  with HELLP, platelet transfusion should be considered prior to vaginal delivery if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy (II-2D; Low/Weak).
5. For a platelet count of  $\geq 50 \times 10^9/L$  with HELLP, platelet transfusion and/or packed red blood cells should be considered prior to either Caesarean or vaginal delivery only if there is excessive active bleeding, known platelet dysfunction, a rapidly falling platelet count, or coagulopathy (IIIB; Low/Weak).
6. We do not recommend corticosteroids for treatment of HELLP until they have been proven to decrease maternal morbidity (II-3L; Low-Moderate/Weak).
7. We recommend against plasma exchange or plasmapheresis for HELLP, particularly within the first four days postpartum (II-3E; Low/Strong).

### Comments

HELLP syndrome must be differentiated from other 'imitators' (see 'Investigations to diagnosis the HDP, When preeclampsia is suspected').

Table 9 presents platelet transfusion recommendations for HELLP [468,469], as platelet counts  $<10-20 \times 10^9/L$  increase the risk of profound haemorrhage even with non-operative delivery [470]. The platelet count may decrease rapidly in HELLP, mandating frequent serial measurement of platelet count (within hours), depending on the clinical condition. Clinicians should be aware of the potential for delays when ordering platelets or other blood products. Anti-D(Rho) sensitization can be prevented by anti-D prophylaxis (300 µg dose anti-D immune globulin) in Rh D negative women [470].

HELLP does not improve immediately after delivery [471], as most women's platelet counts fall and liver enzymes rise until day two postpartum, usually improving by day four such that by day six (or within 3 days of the platelet nadir), the platelet count should be  $\geq 100 \times 10^9/L$ .

For HELLP, corticosteroids (dexamethasone more than betamethasone), especially if initiated before delivery, significantly improve platelet counts and other haematological and biochemical indices (ALT, AST, and LDH), but without a significant impact on major maternal or perinatal outcomes (death or severe morbidity) [472]. Regional anaesthesia may be achieved more often with corticosteroids [473]. By incorporating dexamethasone into a local HELLP protocol (along with  $MgSO_4$  and antihypertensives), one centre noted less severe maternal morbidity and disease progression [474].

Women with progressive HELLP, particularly postpartum, may improve with plasma therapies effective for thrombotic thrombocytopenic purpura (TTP) [475]. No RCTs were identified.

Also, see 'Timing of delivery'.

### Postpartum treatment

#### Care in the 6 weeks post partum

#### Recommendations

1. BP should be measured during the time of peak postpartum BP, at days three to six after delivery (III-B; Low/Strong).

**Table 9**

Recommendations about TRANSFUSION of platelets related to mode of delivery in HELLP.

Platelet count	Mode of delivery	
	Cesarean delivery	Vaginal delivery
$<20 \times 10^9/L$	Recommend	Recommend
$20-49 \times 10^9/L$	Recommend	Consider in presence of: <ul style="list-style-type: none"> <li>• Excessive active bleeding</li> <li>• Known platelet dysfunction</li> <li>• Platelet count falling rapidly</li> <li>• Coagulopathy</li> </ul>
$\geq 50 \times 10^9/L$	Consider in presence of: <ul style="list-style-type: none"> <li>• Excessive active bleeding</li> <li>• Known platelet dysfunction</li> <li>• Platelet count falling rapidly</li> <li>• Coagulopathy</li> </ul>	Consider in presence of: <ul style="list-style-type: none"> <li>• Excessive active bleeding</li> <li>• Known platelet dysfunction</li> <li>• Platelet count falling rapidly</li> <li>• Coagulopathy</li> </ul>
Regardless of the platelet count	No platelets should be transfused if there is a strong suspicion of HIT or TTP-HUS	

HIT, heparin-induced thrombocytopenia; TTP-HUS, thrombotic thrombocytopenic purpura – haemolytic uraemic syndrome.

2. Women with postpartum hypertension should be evaluated for pre-eclampsia (either arising *de novo* or worsening from the antenatal period) (II-2 B; Low/Weak).
3. Consideration should be given to continuing antihypertensive therapy postpartum, particularly in women with antenatal preeclampsia and those who delivered preterm (II-2I; Low/Weak).
4. Severe postpartum hypertension must be treated with antihypertensive therapy, to keep sBP <160 mmHg and diastolic BP <110 mmHg (IA; Moderate/Strong).
5. In women without co-morbidities, antihypertensive therapy should be considered to treat non-severe postpartum hypertension to keep BP <140/90 mmHg (III-I; Very low/Weak).
6. Women with co-morbidities other than pre-gestational diabetes mellitus should be treated to keep BP <140/90 mmHg (III-C; Very low/Weak).
7. Women with pre-gestational diabetes mellitus should be treated to keep BP <130/80 mmHg (III-C; Very low/Weak).
8. Antihypertensive agents generally acceptable for use in breastfeeding include the following: nifedipine XL, labetalol, methyldopa, captopril, and enalapril (III-B; Moderate/Weak).
9. There should be confirmation that end-organ dysfunction of preeclampsia has resolved (III-C; Very low/Strong).
10. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be given postpartum if hypertension is difficult to control, there is evidence of kidney injury (oliguria and/or an elevated creatinine) ( $\geq 90 \mu\text{M}$ ) or platelets are <50–109/L (III-C; Low/Weak).
11. Postpartum thromboprophylaxis should be considered in women with preeclampsia, particularly in the presence of other risk factors (II-2B; Low/Weak).

#### Comments

*Postpartum hypertension.* Hypertension may antedate delivery in up to 50% of women with postpartum hypertension. Women with pre-existing hypertension not requiring antihypertensives antenatally may require antihypertensives early in the puerperium [476]. Those at greatest risk of postpartum hypertension are those who delivered preterm, and, for multiparous women, those with higher urate levels [477,478]. Postpartum deterioration of maternal end-organ function occurs in up to 25%, usually in the early puerperium, especially with severe disease [479].

*De novo* postpartum hypertension is most common on days three to six [480]. It may be isolated or associated with preeclampsia-related end-organ dysfunction. Two thirds of women with postpartum preeclampsia had no antenatal HDP and their postpartum preeclampsia/eclampsia usually develops within days, but occasionally up to three weeks, after delivery [481].

*Management.* There are no reliable data to guide whether or not antenatal antihypertensives should be continued postpartum, and which antihypertensive to choose.

All severe hypertension should be treated, be it antenatal or postpartum. Based on non-pregnancy data, BP should

be treated to <140/90 mmHg in women with a co-morbid condition, and further to <130/80 mmHg in women with *pre-gestational* diabetes mellitus [7].

There is no clear best choice of agent [482]. Antihypertensives used most commonly in pregnancy, as well as captopril and enalapril are “usually acceptable” for breastfeeding [483,484], but caution may be exercised in preterm and low birth weight infants due to immature drug clearance and/or increased susceptibility to drug effects. Generally, antihypertensives are needed longer in women with preeclampsia ( $\approx 2$  weeks) vs. gestational hypertension ( $\approx 1$  week) [18].

*Postpartum analgesia.* Non-steroidal anti-inflammatory drugs (NSAIDs), often self-administered analgesics, may exacerbate hypertension or cause acute kidney injury, and may best be avoided with resistant hypertension, high serum creatinine, or low platelet counts [485].

*Postpartum thromboprophylaxis.* Thromboprophylaxis use should be based on number of thromboembolic risk markers, especially preeclampsia associated with adverse perinatal outcome, advanced maternal age, obesity, prolonged antenatal bed rest, postpartum haemorrhage, and emergency Caesarean delivery [297,486,487]. The duration of thromboprophylaxis may vary from until full mobilization to 4–6 weeks postpartum (also, see ‘Anaesthesia’).

#### Care beyond 6 weeks post partum

#### Recommendations

1. Women with a history of severe preeclampsia (particularly those who presented or delivered before 34 weeks’ gestation) should be screened for pre-existing hypertension and underlying renal disease (II-2B; Low/Weak).
2. Referral for internal medicine or nephrology consultation (by telephone if necessary) should be considered for women with: (i) postpartum hypertension that is difficult to control, or (ii) women who had preeclampsia and have at 3–6 months postpartum either ongoing proteinuria, decreased eGFR (<60 ml/min), or another indication of renal disease (such as abnormal urinary sediment) (III-A; Low/Weak).
3. Women who are overweight should be encouraged to attain a healthy body mass index to decrease risk in future pregnancy (II-2A; Moderate/Strong) and for long-term health (I-A; Low-moderate/Strong).
4. Women with pre-existing hypertension or persistent postpartum hypertension should undergo the following investigations (if not done previously) at least 6 weeks postpartum: urinalysis; serum sodium, potassium and creatinine; fasting glucose; fasting lipid profile; and standard 12-lead electrocardiography (III-I; Low/Weak).
5. Women who are normotensive but who have had a HDP, may benefit from assessment of traditional cardiovascular risk markers (II-2B; Low-moderate/Weak).
6. All women who have had a HDP should pursue a healthy diet and lifestyle (I-B; Low/Weak).

### Comments

Gestational hypertension usually resolves by 6 weeks postpartum, while the hypertension of severe preeclampsia may take 3–6 months [488]. Routine measurement of microalbuminuria after preeclampsia resolution is not recommended without a specific renal indication. Any abnormalities should prompt further investigation and appropriate specialist referral.

*Future pregnancy.* Screening for other underlying causes of preeclampsia (e.g., renal disease) may better inform management of the woman's health between (or after) pregnancies, or in subsequent pregnancies. Thrombophilia confers, at most, a weakly increased risk of preeclampsia (and other placentally mediated pregnancy complications), and thrombophilia screening following preeclampsia is not recommended [489]. One exception may be preeclampsia with delivery at <34 weeks following which testing for antiphospholipid antibodies could be undertaken to diagnose the antiphospholipid syndrome [490].

*Long-term maternal health.* Any weight gain between pregnancies predicts preeclampsia and other pregnancy complications [491]. Observational data suggest that in women who are morbidly obese, bariatric surgery lowers rates of subsequent HDP [492].

Women with pre-existing hypertension should receive recommended cardiovascular risk factor screening and treatment [493].

As pregnancy is a biological 'stress test' of sorts, women with a prior HDP (particularly associated with preterm delivery or adverse perinatal outcome) should be informed of their increased future health risks, including; hypertension; cardiovascular and cerebrovascular morbidity and mortality; subsequent renal disease; thromboembolism; hypothyroidism; and type 2 diabetes mellitus [494–503]. It is unclear whether the microalbuminuria associated with previous preeclampsia represents underlying renal disease or is an independent cardiovascular risk marker [504]. That early testing (and intervention) for cardiovascular and renal risk factors will improve cardiovascular outcomes is unproven.

Barriers to compliance with a healthy diet and lifestyle include poor postpartum physical and psychological recovery, and lack of postpartum medical and psychological support from healthcare providers [505].

*Long term offspring health.* Be aware of a growing literature describing adverse effects of preeclampsia on offspring cardiovascular [506] and reproductive health [507].

### Effects of maternal hypertension and its' therapies on child neurobehavioral development

#### Recommendations

1. Clinicians should be aware that gestational hypertension and preeclampsia may each be associated with an increase in adverse paediatric neurodevelopmental effects, such as inattention and externalizing behaviours (e.g., aggressiveness) (II-2-B; Very low/Weak).

2. Clinicians should be reassured that there is no compelling evidence that antihypertensive medications (specifically labetalol, nifedipine, or methyldopa) are themselves associated with clear adverse neurodevelopmental effects (I-B; Low/Weak).

#### Comments

Superimposed preeclampsia (vs. pre-existing hypertension alone) has no adverse effect on (or slightly better) intellectual development (no information given on antihypertensives) [508].

Gestational hypertension and preeclampsia may predict generally modest long term effects on child development. Children of women with preeclampsia had *reduced* internalizing morbidity (e.g., anxiety) at ages 5 and 8 years, but children of women with gestational hypertension were more likely to have poorer behaviour from 8 years onwards, with the largest difference seen at 14 years (no information given on antihypertensives) [509]. Both types of HDP were associated with a small reduction in verbal ability of uncertain clinical significance [510]. Little information was provided on antihypertensives which were considered as a covariate. Babies of antihypertensive (mainly methyldopa)-treated mothers (vs. normtensive controls) have excess delayed fine-motor function at 6 months of age, while those of placebo-treated hypertensive mothers more frequently had 'questionable' neurological assessment and delayed gross-motor function at 12 months [511]. However other small RCTs of methyldopa [512], atenolol [347], and nifedipine [513] did not observe negative impacts on child development. Methyldopa (but not labetalol) may be associated with lower IQ; the duration of treatment being an independent negative predictor of children's Performance IQ [514].

## Chapter 4: Patient perspective

### Recommendations

1. Health care providers should be alert to symptoms of post-traumatic stress following a HDP; and refer women for appropriate evaluation and treatment (II-2B; Low/Weak).
2. Health care providers should inform their patients, antepartum and postpartum, about pre-eclampsia, its signs and symptoms, and the importance of timely reporting of symptoms to health care providers (II-2; Very low/Weak).
3. Information should be re-emphasized at subsequent visits (III-C; Very low/Weak).

#### Comments

We support incorporating the patient perspective into care. Engaged patient advocacy organizations are the Preeclampsia Foundation ([www.preeclampsia.org/](http://www.preeclampsia.org/)), Action on Pre-eclampsia (APEC) ([www.apec.org.uk/](http://www.apec.org.uk/)), Australian Action on Pre-eclampsia (AAPEC) ([www.aapec.org.au/](http://www.aapec.org.au/)), New Zealand Action on Pre-eclampsia (NZ APEC) ([www.nzapec.com/](http://www.nzapec.com/)), and Association de Prevention et d'Actions contre la pre-eclampsie (APAPE) ([www.eclampsie.moonfruit.fr/](http://www.eclampsie.moonfruit.fr/)) [515]. The Preeclampsia Foundation advocates for: better patient (and health care provider) education about the antenatal, early postnatal and long-term maternal implications

of preeclampsia; an emphasis on early maternal signs and symptoms of preeclampsia; better doctor–patient communication about preeclampsia; and evidence-based guidelines for pre-eclampsia screening, detection; and management [515].

#### *Post traumatic stress*

There is growing evidence that women may experience post-traumatic stress disorder up to seven years postpartum [516–524], the prevalence of symptoms being highly variable, ranging from the minority to the majority of women, and higher after: maternal hospitalization >7 days, HDP onset/delivery preterm, NICU admission, adverse neonatal outcomes, and uncertainty about the child's long-term health [519]. Symptoms are not specific to the HDP, and follow preterm delivery for other indications [520]. Although post-traumatic stress symptoms do not have an impact on infant cognitive or psychomotor development at one year of age, maternal symptoms are amenable to clinical psychological therapy, and earlier referral may abbreviate treatment [523].

Women and their maternity care providers seem to view experiences of preeclampsia differently. For health-care professionals, preeclampsia represented the care that must be delivered, primarily responding to the biology of preeclampsia. For women, generally lacking knowledge and understanding about pre-eclampsia, preeclampsia represented fear and risk [525].

#### *Patient education and engagement*

In a survey of women who had experienced preeclampsia, eclampsia and/or HELLP, preeclampsia was viewed as very important to all and traumatic to many respondents, women, their partners, close relatives, or friends. The provision of information and support was valued prior to, and at the time of, diagnosis as well as being revisited during ongoing care [526].

Women are not knowledgeable about the HDP, even with pre-existing hypertension, and are not satisfied with the medical information they receive, suggesting that clinicians should both place more value on informing women about their disease and its potential course, and check that women have understood the information [527,528]. Although limited health literacy may complicate risk communication, tools have been developed for such purposes [527,528].

Women enjoy participating in aspects of their care, be it receiving information as study participants [529], or participating in management of their BP [530]. They do not object to being randomized [380].

Women have expressed a preference for home or day care [531] and self (rather than 24-h ambulatory) BP monitoring [532].

### **Chapter 5: Knowledge Translation tools and implementation of the guideline**

#### *Knowledge translation tools*

Table 10 lists tools to support the application of this guideline. Some websites provide general information about BP measurement for non-pregnant patients, but the recommendations are similar enough to those in pregnancy to be useful. Patients, their partners and care

providers should be well educated about the HDP and relevant sites are listed.

#### *Implementation of the guideline*

Implementation of any evidence depends on individual knowledge and beliefs, as well as institutional culture. Strong recommendations should be incorporated into clinical practice. In well-resourced settings, almost all preeclampsia-related maternal deaths involve substandard care [534].

Some recommendations may require additional effort to implement, as highlighted below.

- One of the new recommendations regarding blood pressure devices is: 'The accuracy of all BP measurement devices used in hospitals or offices should be checked regularly against a **calibrated device**.' This might be something that not all Canadian hospitals and offices do on a regular basis.
- Physicians should consider the category 'other HDP' (which constitutes white coat and masked hypertension) as part of the classification of hypertensive women and consider using some form of out of office BP measurement to evaluate women with non-severe pre-existing or gestational hypertension.
- Health care providers should inform pregnant women about the symptoms and signs of the HDPs and refer them to appropriate knowledge translation tools.
- We recommend the use of corticosteroids for women at  $\leq 34^6$  weeks who are at high risk of delivery within the next seven days. This gestational age cut-off represents a fundamental change in practice that will require discussion.
- Physicians should be familiar with blood bank policies of their own hospital.
- Physicians should be aware of postpartum signs of maternal post traumatic stress disorder and maternal and perinatal long term effects of HDPs, especially as this is a 'vulnerable' time in maternal care when the maternity care provider is often handing back care to the primary care physician.

### **Chapter 6: Future directions**

There are many areas in which important research is pending, such as the CHIPS trial of antihypertensive therapy and its impact on perinatal and maternal outcomes and the TIPPS trial of heparin thromboprophylaxis to prevent recurrent placental complications (including preeclampsia). There are also many important research questions for which answers are currently unavailable. Clinicians are encouraged to participate in clinical research. If the paediatric oncology research network can enrol more than 60% of their patients in RCTs, then the maternity care community should be able to improve on the <10% recruitment rate of women by incorporating clinical research into medical practice [535].

#### **Ethics statement**

These recommendations have been reviewed and approved by the Hypertension Guideline, Maternal Fetal

**Table 10**  
Knowledge translation tools for HDP.

Tool	Resource	Comment
<i>Patient information</i>		
<b>BP measurement by patients</b>		
Canadian Hypertension Education Program (CHEP)	<a href="http://www.hypertension.ca/measuring-blood-pressure">http://www.hypertension.ca/measuring-blood-pressure</a> (English) <a href="http://www.hypertension.ca/fr/mesures-dp1">http://www.hypertension.ca/fr/mesures-dp1</a> (French)	This website gives patients basic information about BP measurement and gives instructions on self-measurement
National Heart Foundation of Australia	<a href="http://www.heartfoundation.org.au/SiteCollectionDocuments/Self-Management-BP.pdf">http://www.heartfoundation.org.au/SiteCollectionDocuments/Self-Management-BP.pdf</a>	This website gives information about the self measurement of BP by patients and advice about buying a machine
Heart and Stroke Foundation	<a href="https://ehealth.heartandstroke.ca/heartstroke/bpap.net/vid_measure_bp.html">https://ehealth.heartandstroke.ca/heartstroke/bpap.net/vid_measure_bp.html</a>	This link refers to a movie that gives instructions for self measurement of BP
Société canadienne d'hypertension	<a href="http://hypertension.ca/measuring-blood-pressure">http://hypertension.ca/measuring-blood-pressure</a> <a href="http://hypertension.ca/fr/mesures-dp1">http://hypertension.ca/fr/mesures-dp1</a>	Detailed information in English and French (with a poster in English) although the images are of older patients
Canadian Hypertension Education Program (CHEP) Brochure	<a href="https://www.youtube.com/watch?v=eqajdX5XU9Y&amp;feature=plcp">https://www.youtube.com/watch?v=eqajdX5XU9Y&amp;feature=plcp</a> RCOG.org.uk	Detailed video on home BP measurement (outside pregnancy) This also includes your risk of recurrence
<b>BP measurement and pre-existing hypertension</b>		
Heart and Stroke Foundation	<a href="http://www.heartandstroke.ca">www.heartandstroke.ca</a>	This website gives information about hypertension outside of pregnancy, blood pressure monitoring and medication
<b>Impact of pre-existing hypertension on pregnancy</b>		
American Heart Association document: Chronic Hypertension in Pregnancy	[533]	This document explains in an understandable way how chronic hypertension and pregnancy influence each other and what the symptoms of preeclampsia that women should be aware of
<b>Preeclampsia awareness</b>		
Preeclampsia Education Tool	Preeclampsia Foundation  <a href="http://www.preeclampsia.org/market-place">http://www.preeclampsia.org/market-place</a>	This tool explains the risks and symptoms of preeclampsia and how to act on them. This tool has shown to be effective in improving patient knowledge in a RCT (120 women) [528]
Educational magnets and symptom Pads	Preeclampsia Foundation <a href="http://www.preeclampsia.org/market-place">http://www.preeclampsia.org/market-place</a>	Quick checklists of signs and symptoms of preeclampsia
<b>Patient education once preeclampsia develops</b>		
Brochures:	Preeclampsia Foundation <a href="http://www.preeclampsia.org/market-place">http://www.preeclampsia.org/market-place</a>	These are available in English and Spanish
<ul style="list-style-type: none"> <li>• HELLP syndrome</li> <li>• Preeclampsia FAQ</li> <li>• Preeclampsia and heart diseases</li> </ul>		
Hôpital Maisonneuve-Rosemont, Centre affilié à l'Université de Montréal: Brochure on pre-eclampsia.	<a href="http://biblio.hmr.qc.ca/Publications_pdf/H/hypertension_sfe080.pdf">http://biblio.hmr.qc.ca/Publications_pdf/H/hypertension_sfe080.pdf</a>	French brochure for patients about preeclampsia
<b>Patient education after preeclampsia</b>		
Educational pamphlet	Preeclampsia Foundation APEC	Educational brochure about cardiovascular risks associated with preeclampsia
<i>Health care provider information</i>		
<b>BP measurement</b>		
WHO document: detecting preeclampsia, a practical guide, 2005	<a href="http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/MSM_92_3_/en/index.html">http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/MSM_92_3_/en/index.html</a>	This document contains instructions how to measure blood pressure and proteinuria in pregnant women, and how to diagnose hypertensive disorders in pregnancy. This tool is for health care providers
<b>Approved BP measurement devices</b>		
Canadian Hypertension Education Program (CHEP) Educational Trust	<a href="http://www.hypertension.ca/devices-endorsed-by-hypertension-canada-dp1">http://www.hypertension.ca/devices-endorsed-by-hypertension-canada-dp1</a> <a href="http://www.dableducational.org/sphygmomanometers/devices_1_clinical.html">http://www.dableducational.org/sphygmomanometers/devices_1_clinical.html</a>	This website gives an oversight of recommended blood pressure devices This website gives an oversight of recommended blood pressure devices, outside of and during pregnancy
<b>Clinical practice guidelines from other countries</b>		
NICE guidelines (UK, 2010)	<a href="http://www.nice.org.uk/nicemedia/live/13098/50475/50475.pdf">http://www.nice.org.uk/nicemedia/live/13098/50475/50475.pdf</a>	Graded recommendations
Australasian guidelines (Australia and New Zealand, 2008) American guidelines WHO guidelines	<a href="http://www.somanz.org/pdfs/somanz_guidelines_2008.pdf">http://www.somanz.org/pdfs/somanz_guidelines_2008.pdf</a> [98] <a href="http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf">http://whqlibdoc.who.int/publications/2011/9789241548335_eng.pdf</a>	Very practical but evidence not graded

Medicine and Family Physician Advisory Committees, and Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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### Competing interests

PVD is a paid consultant of Alere International for work not related to the current manuscript.

### Appendix A

#### Appendix Table A1

Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care.

Quality of evidence assessment <sup>*</sup>	Classification of recommendations <sup>†</sup>
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in the category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

<sup>\*</sup> The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.

<sup>†</sup> Recommendations included in these guidelines have been adapted from the Classification of recommendations criteria described in The Canadian Task Force on Preventive Health Care [5].

#### Appendix Table A2

GRADE definitions for quality of evidence and strength of recommendations [6].

Quality of the evidence	
<b>High</b>	We are very confident that the true effect lies close to that of the estimate of the effect
<b>Moderate</b>	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
<b>Low</b>	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect
<b>Very low</b>	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect
Strength of recommendations	
<b>Strong</b>	
<i>For patients/public</i>	We believe most people in this situation would want the recommended course of action and only a small number would not
<i>For clinicians</i>	The recommendation would apply to most individuals. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences
<i>For policy makers and developers of quality measures</i>	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator
<b>Weak</b>	
<i>For patients/public</i>	We believe that most people in this situation would want the recommended course of action, but many would not. Different choices are acceptable for each person and clinicians should support patients and discuss their values and preferences to reach a decision. Decision aids may support people in reaching these decisions
<i>For clinicians</i>	We recognize that different choices may be appropriate for individual patients. Clinicians should support each patient in reaching a management decision consistent with his or her values and preferences. Decision aids may support individuals in reaching such decisions
<i>For policy makers and developers of quality measures</i>	Policy-making will require substantial debate and involvement of various stakeholders. An appropriately documented decision making process could be used as quality indicator

### Disclaimer

This document reflects emerging clinical and scientific advances and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed. Local institutions can dictate amendments to these opinions. They should be well documented if modified at the local level.

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