3

Classification of the hypertensive disorders of pregnancy

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SYNOPSIS

During pregnancy, it is important to detect hypertension of any sort, as pregnancy hypertension is associated with increased maternal and perinatal risks. However, not all hypertensive disorders of pregnancy carry the same level of risk for women and their babies. Therefore, the classification of the hypertensive disorders of pregnancy into pre-existing (chronic) hypertension, gestational hypertension, pre-eclampsia, white coat hypertension and masked hypertension matters. Reducing the rates of false-positive and false-negative classification relative to current standard of care should help to better target health care spending and lower overall costs associated with the care of women with pre-eclampsia. Although classification of the hypertensive disorders of pregnancy is usually straightforward in higher income countries, this may not be the case in settings where late gestational age at booking is prevalent, and the final diagnosis may only be possible at 6 weeks postpartum. Also, as it is critical to identify women who require delivery, the only way to initiate the cure for pre-eclampsia, we endorse the Canadian approach of defining 'severe' pre-eclampsia according to the presence of severe complications that mandate delivery.

As pre-eclampsia is the most dangerous of the hypertensive disorders of pregnancy, tools have been developed in all settings to facilitate identification of women at highest risk of adverse outcomes: miniPIERS for under-resourced settings and fullPIERS for well-resourced settings; both models are optimised by pulse oximetry. There is a need to evaluate how new diagnostic and risk-stratifying biomarkers can be incorporated into existing protocols and to make these biomarkers available as point-of-care tests in all clinical settings.

INTRODUCTION

The purpose of classifying diseases is to facilitate communication among caregivers, and to create meaningful groups with different prognoses, considerations for surveillance, and/or outcomes[1]. As such, the hypertensive disorders of pregnancy are classified in Canada as pre-existing hypertension, gestational hypertension, pre-eclampsia, or 'other' (Table 3.1). A final diagnosis of the type of hypertensive disorder of pregnancy is retrospective, following the postpartum period. Pre-existing hypertension is often called chronic hypertension in other clinical practice guidelines (see "What international guidelines say" below).

The provision of antenatal care using the Scottish paradigm of accelerating frequency of visits towards term was developed, in large part, to facilitate the diagnosis of pre-eclampsia[2]. The full implementation

Table 3.1 Classification of the hypertensive disorders of pregnancy (reproduced with permission by the SOGC)[60]

	Comments
Pre-existing (chronic) hypertension	
	This is defined as hypertension that was present either pre-pregnancy or that develops at $<20^{+0}$ weeks gestation
With comorbid conditions(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 pre-eclampsia	This is also know as 'superimposed pre-eclampsia' and is defined by the development of one or more of the following at ≥20 weeks: • Resistant hypertension, *or* • New or worsening proteinuria, *or* • One/more adverse condition(s)¥ *or* • One/more severe complication(s)¥ Severe pre-eclampsia is defined as pre-eclampsia with one or more severe complication(s)
Gestational hypertension	
	This is defined as hypertension that develops for the first time at $\geq 20^{+0}$ weeks' gestation
With comorbid conditions(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 pre-eclampsia	Evidence of pre-eclampsia may appear weeks after the onset of gestational hypertension
Pre-eclampsia	
	Pre-eclampsia may arise *de novo*. It is defined by gestational hypertnesion and one or more of the following: • New proteinuria, *or* • One/more adverse condition(s)¥ *or* • One/more severe complication(s)¥ Severe pre-eclampsia is defined as pre-eclampsia with one or more severe complication(s)
*'Other hypertensive effects'**	
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; dBP, diastolic BP; HBPM, home BP monitoring; sBP, systolic blood pressure after monitoring

* These may occur in women whose BP is elevated at $<20^{+0}$ or $\geq 20^{+0}$ weeks who are suspected at having pre-existing or gestational hypertension/pre-eclampsia, respectively

¥ Please see Table 3.2 for definitions of adverse conditions and severe complications of pre-eclampsia

of this paradigm was associated with reduced maternal mortality in the United Kingdom since the early 1900s and in Sri Lanka half a century later[2,3].

For pre-existing and gestational hypertension, there are two subgroups[2]: with comorbid conditions, because they constitute indications for tighter blood pressure control outside pregnancy, and evolution of disease can be more difficult to determine; and with pre-eclampsia, because it is associated with the greatest maternal and perinatal risks. Of women under 30 years of age, 1% are hypertensive, and approximately 1% of pregnancies

KEY POINT

In our opinion, the term 'pregnancy-induced hypertension,' or PIH, should no longer be used. In North America, PIH is used as a synonym for pre-eclampsia, whereas in the UK it means gestational hypertension *without* proteinuria. As such, the term has become debased, and may lead to confusion between clinicians

are complicated by pre-existing hypertension, 5–6% by gestational hypertension without proteinuria, and 1–2% by pre-eclampsia[4,5]. The incidence of the hypertensive disorders of pregnancy can be expected to increase in settings where there is a trend towards an older and more obese maternity population.

PRE-EXISTING (OR CHRONIC) HYPERTENSION

Pre-existing hypertension is defined as that which either pre-dates pregnancy or appears before 20^{+0} weeks of pregnancy. Pre-existing hypertension is associated with adverse outcomes for both mother and baby. For the mother, the following risks are heightened: superimposed pre-eclampsia (approximately 20%)[6–19], half of which develops at term[8,14,15,19,20], preterm delivery (about 33%)[6–8,10,12–19], and placental abruption (1.8%). Babies born to women with pre-existing hypertension are also at increased risk of acute or chronic hypoxia/acidosis. Approximately 15% of these babies are born small for gestational age (SGA)[8,10,11,13,14,16–19,21–27]. In a secondary analysis of women with singleton pregnancies and chronic hypertension diagnosed before 20 weeks in the National Institutes of Child Health and Development aspirin trial[28], the risks of adverse pregnancy outcomes increased with increasing blood pressure[29].

It is important to recognise that stillbirth risk reaches 0.1% by 36 weeks in pregnancies complicated by hypertension, similar to that reached at 41 weeks in low-risk pregnancies to justify labour induction[30]. Up to 50% of these newborns are admitted to high-level NICU care because of short-term complications, such as hypothermia, respiratory failure and feeding problems[15].

Women with comorbid conditions are highlighted because they may warrant special blood pressure treatment thresholds, particularly if the comorbid condition is type I or II (but not gestational) diabetes. Other comorbid conditions include major cardiovascular risk factors other than diabetes, renal parenchymal disease, vascular disease, or cerebrovascular disease. (For further discussion of antihypertensive therapy see Chapter 8.)

GESTATIONAL HYPERTENSION

Gestational hypertension is defined as hypertension that appears at $\geq 20^{+0}$ weeks, without the occurrence of proteinuria. However, using ambulatory blood pressure monitoring (ABPM), a 'white coat' effect is seen among about 30% of women diagnosed with hypertension at ≥20 weeks, and this rises to approximately 70% by the third trimester[31]. (For discussion of 'white coat' effect, see Chapter 1.)

Women with gestational hypertension have maternal and perinatal risks that are highly dependent on the gestational age at presentation and the progression to pre-eclampsia. When gestational hypertension appears before 34^{+0} weeks, approximately 35% of women develop pre-eclampsia with the associated heightened risks of maternal and perinatal complications[26,32–36]. Development of that pre-eclampsia takes an average of about 5 weeks[35,36].

For a discussion of the impact of comorbid conditions on recommendations for antihypertensive therapy see Chapter 8.

PRE-ECLAMPSIA

The term pre-eclampsia continues to be widely used internationally. It is widely recognised to be the hypertensive disorder of pregnancy associated with the greatest maternal and perinatal risks, particularly when it is severe in nature and/or presents before 34 weeks. In the latter case, a stillbirth rate of about 10% and a perinatal mortality rate of at least 5% have been reported[37]. The risk of small-for-gestational age (SGA) is also primarily concentrated in cases presenting at <34 weeks, while there is an increased number of large-for-gestational age (LGA) fetuses at term[37–39].

The origins of pre-eclampsia

As long ago as 1996, Ness and Roberts stated:

> "The cause of preeclampsia remains elusive in spite of many attempts to understand its biologic characteristics and to characterize its predictors. We suggest that there are distinct origins of preeclampsia, each with its own pathologic characteristics and natural history. One genesis is the result of reduced placental perfusion, which we will call placental, and another results from maternal disorders pre-existing (but sometimes not evident before) pregnancy. These pre-existing maternal disorders comprise predisposing factors for cardiovascular disease such as hypertension, renal disease, overweight, and diabetes."[40]

Over the past two decades, the amount of evidence to support this hypothesis has grown, leading more to pre-eclampsia being a pregnancy-specific inflammatory disorder of variable pathogenesis. We will share two examples of probable pathways to disease, summarised in Figure 3.1[41].

Angiogenic factor imbalance, with an excess of circulating anti-angiogenic factors (e.g., soluble fms-like tyrosine kinase (sFlt)-1 and soluble endoglin) and a reduction in pro-angiogenic factors (e.g., placental growth factor (PlGF)), has a clear role in identifying pregnancies complicated by placental underperfusion, be that manifested as pre-eclampsia or normotensive intrauterine growth restriction[42–45]. This angiogenic imbalance appears to be predictive of early-onset (at or before 34 weeks of pregnancy), primarily placental underperfusion-related, pre-eclampsia that is more dangerous to the individual woman with the condition, as demonstrated in both well- and under-resourced settings[41,46–48]. It may be of particular importance in identifying women with pre-existing medical conditions, especially renal disease, who have developed superimposed pre-eclampsia[49–51]. As yet, it is unclear why some women with angiogenic factor imbalance develop pre-eclampsia, while others remain normotensive, but the concentration of circulating placental debris may be an example of an important co-factor in stimulating the clinical syndrome of pre-eclampsia[52].

Data from the SCOPE (Screening for Pregnancy Endpoints) Consortium show that late-onset

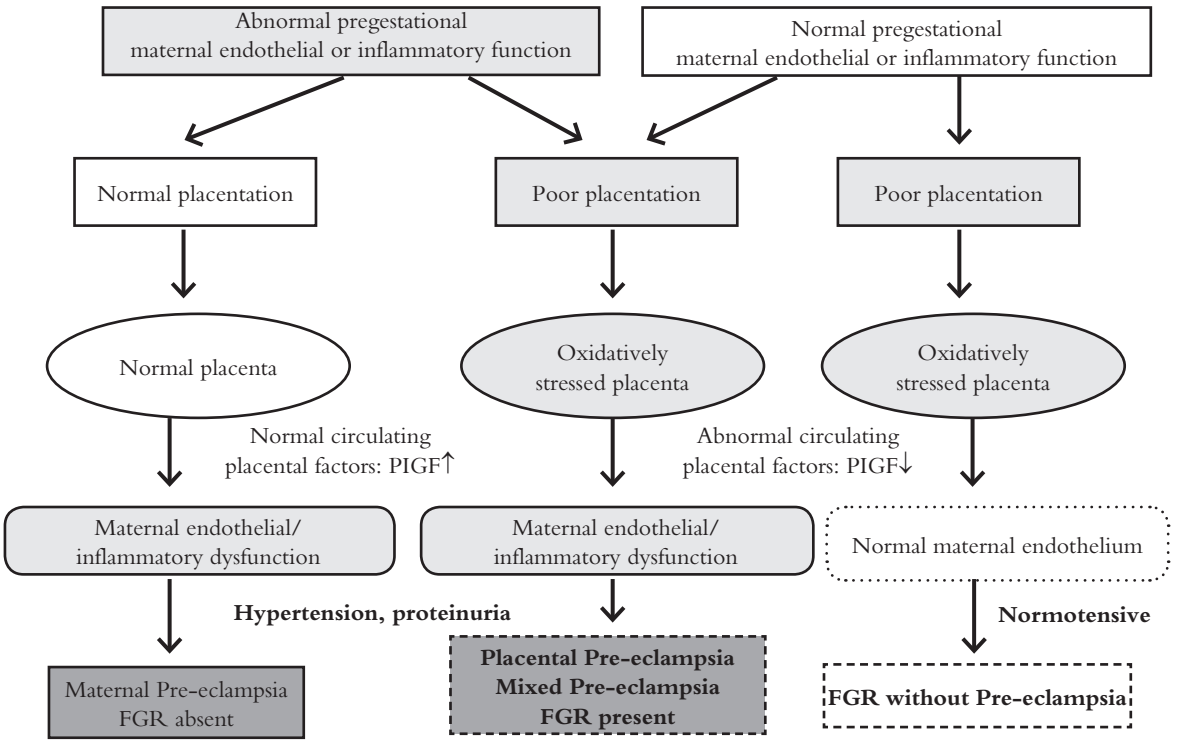

Figure 3.1 A model of pre-eclampsia (reproduced with permission from Staff AC *et al. Hypertension* 2013[41]). FGR, fetal growth restriction; PIGF, placental growth factor

pre-eclampsia is more closely related to factors that predict later cardiovascular disease through the metabolic syndrome[53,54], the so-called "maternal pre-eclampsia." Reflecting these findings, point-of-care assessment with glycosylated fibronectin, a strong marker of the risk of gestational diabetes and management, may provide a readily available method of confirming the diagnosis of "maternal" pre-eclampsia[55].

Clearly, in some women there is an overlap in precipitating factors. The combined aetiology may become increasingly important in lower-income countries in many of which pre-eclampsia of placental (versus maternal) origin currently predominates. This may be explained by the shorter time between first intercourse, coitarche and first pregnancy, thereby reducing the opportunity for exposure to paternal antigen through exposure to seminal fluid; this reduces the maternal immune adaptiveness that facilitates normal placental development[41,46]. However, pre-eclampsia of maternal origin may increase in prevalence as the obesity epidemic spreads across the globe. In addition, the maternal factors associated with the metabolic syndrome are associated with a pro-inflammatory state[53] that may be amplified by the burden of infectious diseases and chronic inflammation borne by women in less developed countries[56].

Defining pre-eclampsia

All hypertension societies consider pre-eclampsia to be a hypertensive disorder commonly defined by new-onset proteinuria, and possibly other adverse conditions (Table 3.2). A restrictive definition of pre-eclampsia is gestational hypertension with proteinuria, and this is often used by the research community and was endorsed for this purpose by the International Society for the Study of Hypertension in Pregnancy (ISSHP)[57]. The definition of pre-eclampsia as gestational hypertension with proteinuria or typical end-organ dysfunction is generally supported by other clinical practice guidelines (see "What international guidelines say" below)[58], and is likely to reduce maternal and perinatal risks[59].

'Resistant hypertension' is defined as hypertension that requires three concurrent antihypertensive medications for blood pressure control after 20 weeks' gestation. The 'adverse conditions' associated with pre-eclampsia consist of maternal symptoms and signs, abnormal maternal laboratory results, and abnormal fetal monitoring results that may herald the development of more severe complications. They are conditions to which we respond (e.g., low oxygen saturation) in order to avoid end-organ complications of pre-eclampsia (e.g., pulmonary oedema). The adverse conditions are discussed in detail below. This somewhat liberal definition of pre-eclampsia is intended to signal a need for heightened maternal and fetal surveillance, recognising that none of the adverse conditions are specific to pre-eclampsia.

Oedema and weight gain remain excluded from the definition of pre-eclampsia, as neither are significantly associated with perinatal mortality and morbidity[57,61]. Oedema, even facial oedema, is neither sensitive nor specific for pre-eclampsia[46,60,62].

Angiogenic imbalance is yet to be included in the definition. The diagnosis of hypertension and proteinuria are discussed in Chapters 1 and 2.

It should be remembered that pre-eclampsia can arise *de novo* postpartum, a condition that carries similar risks to antenatally detected pre-eclampsia that persists postpartum[63]. Women with *de novo* postpartum pre-eclampsia were included in the miniPIERS and fullPIERS (Pre-eclampsia Integrated Estimate of RISK) studies described in more detail, below[47,48]. (See 'Treatment postpartum' for further detail.)

'Severe' pre-eclampsia

What constitutes 'severe' pre-eclampsia is a matter of international controversy, although multi-organ involvement is the basis for the definition in guidelines from the UK (www.nice.org.uk/guidance)[64], Australasia (http://www.somanz.org/)[65], the United States[62], and the ISSHP[66] (see "What international guidelines say" below for more details)[58].

In Canada, the definition of 'severe' pre-eclampsia was modified to describe pre-eclampsia associated with one or more severe complications (including stillbirth). As such, women with severe pre-eclampsia as defined in Canada require delivery regardless of gestational age. Noticeable differences with other published definitions include the removal of heavy proteinuria as a criterion and the absence of the gestational age criterion present in the American and ISSHP guidelines.

Table 3.2 The adverse conditions that define pre-eclampsia and 'severe' pre-eclampsia according to the SOGC (reproduced with permission from SOGC)[60]

Organ system affected	*Adverse conditionals (that increase the risk of severe complications)*	*Severe complications (that warrant delivery)*
CNS	Headache/visual symptoms	Eclampsia PRES Cortical blindness or retinal detachment Glasgow coma scale <13 Stroke, TIA, or RIND
Cardiorespiratory	Chest pain/dyspnoea Oxygen saturation <97%[76]	Uncontrolled severe hypertension (over a period of 12 h despite use of three antihypertensive agents) Oxygen saturation <90%, need for ≥50% oxygen for >1 h, intubation (other than for Caesarean section), pulmonary oedema Positive inotopic support Myocardial ischaemia or infarction
Haematological	Elevated WBC count Elevated INR or aPTT[74] Low platelet count	Platelet count $<50 \times 10^9$/L Transfusion of any blood product
Renal	Elevated serum creatinine[47] Elevated serum uric acid	Acute kidney injury (creatinine >150 μM with no prior renal disease) New indication for dialysis
Hepatic	Nausea or vomiting RUQ or epigastric pain Elevated serum AST, ALT, LDH, or bilirubin Low plasma albumin[73]	Hepatic dysfunction (INR >2 in absence of DIC or warfarin/coumarin) Hepatic haematoma or rupture
Feto-placental	Non-reassurring FHR IUGR[37] Oligohydramnios Absent or reversed end-diastolic flow by Doppler velocimetry	Abruption with evidence of maternal or fetal compromise Reverse ductus venosus A wave[37] Stillbirth

AST, aspartate aminotransferase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; DIC, disseminated intravascular coagulation; FHR, fetal heart rate; INR, international normalised ratio; LDH, lactate dehydrogenase; PRES, posterior reversible leukoencephalopathy syndrome; RIND, reversible neurological deficit <48 h; RUQ, right upper quadrant; TIA, transient ischaemic attack

HELLP syndrome

While most guidelines identify HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome as a severity criterion, the 2014 Canadian guidelines do not. Why? As practitioners, when we are looking after women remote from term (e.g., <30 weeks' gestation), we offer expectant management to those women who accept this approach after counselling. Rather than wishing to avoid HELLP syndrome, or any of its component criteria, we aim to identify its development as early as possible and to respond to it to avoid more dangerous complications. We recognise that the HELLP syndrome adds risk to a pregnancy[67,68], and, by multivariable regression analysis, both platelet count and AST (aspartate aminotransferase) are independently informative components of the fullPIERS (Pre-eclampsia Integrated Estimate of RiSk) model (see below)[47]. The overlap between, and contrasting features of, HELLP syndrome and acute fatty liver of pregnancy should be considered[69]. Our practice is to include a random glucose in our laboratory assessment of women with suspected or confirmed pre-eclampsia to ensure that acute fatty liver of pregnancy does not go unrecognised[70,71].

The adverse conditions of pre-eclampsia
(Table 3.2)

In this classification system, we do not include those conditions that are serious end-organ complications of pre-eclampsia (e.g., eclampsia, abruption, pulmonary oedema, and stillbirth). These are complications that can have permanent sequelae and are life-threatening. Clinicians should seek to avoid these complications altogether, rather than await their development and then react with timely delivery. For this reason, reversed end-diastolic flow remains an adverse condition.

We have modified the remaining adverse conditions based on their associations with severe complications. Most of the informative data came from the univariable analyses in the fullPIERS model developed from a cohort of 2024 women admitted to hospital with pre-eclampsia[47,72–82]. As such, we have included in the adverse conditions maternal oxygen saturation, serum uric acid and serum albumin. Although headache and visual symptoms were not associated with severe complications in fullPIERS (*p* values of 0.30 and 0.96, respectively), we have retained them for face validity until the fullPIERS model can be externally validated.

We have noted but not added as adverse conditions other risk factors for severe complications among women with pre-eclampsia: young maternal age, maternal age ≥35 years in nullipara, immigrant status, nulliparity, extremes of maternal weight and, in the index pregnancy, multiple pregnancy and lower gestational age at presentation (so-called 'early' pre-eclampsia)[47,48,80–82].

In development of the fullPIERS model, oliguria was not examined as a predictor of adverse maternal (or perinatal) outcome. Oliguria is measurable in women who are hospitalised with pre-eclampsia (most accurately with an indwelling catheter) and is defined as <15 mL/h for 6 consecutive hours[83]. Oliguria is commonly observed in the hours following either vaginal or Caesarean delivery. Prolonged oliguria (for more than 12–24 hours) is more indicative of renal injury outside pregnancy[83], particularly when associated with a rising serum creatinine.

Each adverse condition is not associated with the same risk of severe complications. In the fullPIERS model, the following were *independently* associated with adverse maternal outcomes: preterm pre-eclampsia, chest pain or dyspnoea, or an abnormality of any of: oxygen saturation by pulse oximetry, platelet count, serum creatinine, or AST[47]. In fact, only pulse oximetry reaches an international standard of independent ability to personalise risk in women with pre-eclampsia as a solo test[76], and is retained in the fullPIERS model. Although other factors such as symptoms of headache and laboratory abnormalities may be predictive of adverse maternal events in univariable analyses[47,48,73–77,79,84–89], they were not independently predictive in the fullPIERS multivariable model[47].

Although an online calculator (www.cfri.ca/piers) is available for entry of continuous variables (like gestational age) into the fullPIERS model, the fullPIERS model must be externally validated before it can be recommended for routine clinical use, whether on admission or over the first 48 hours after admission[78]. Preliminary external validation suggests that the fullPIERS model has clinical utility, especially in women with more severe forms of pre-eclampsia[72].

It may be that factors such as uric acid would become important if the fullPIERS model were recalibrated to include women with the full spectrum of hypertensive disorders of pregnancy[84], another task currently underway. Evolving tests of platelet consumption, such as platelet distribution width may be informative of risk in women with pregnancy hypertension should initial findings be confirmed[90]. How more recently derived markers of platelet consumption (e.g., platelet distribution width) may interact with fullPIERS or have independent predictive ability is uncertain[90]. Definitive temporal and external validation studies of fullPIERS, and testing the interaction between fullPIERS and biomarkers being introduced into clinical practice (see below), are underway.

In a single site study of 46 women with either pre-eclampsia or eclampsia undergoing MRI, predictors specifically of posterior reversible leukoencephalopathy syndrome were younger age, higher systolic and diastolic blood pressures, eclampsia and lower platelets[91].

The associated miniPIERS model[48], which is solely based on demographics, symptoms and signs, is discussed in the "Priorities for under-resourced settings" section below, but may be informative for practitioners who are in well-resourced settings but who do not have immediate recourse to laboratory tests.

As all forms of pregnancy hypertension, especially pre-eclampsia, are risk factors for the development of peripartum cardiomyopathy, the routine use of pulse oximetry and judicious use of cardiac imaging will improve the detection of this life-threatening complication. Women of African and East Asian descent seem particularly prone to peripartum cardiomyopathy[92].

How *maternal* adverse conditions may predict adverse outcomes for the fetus or neonate among women with pre-eclampsia is unclear. The general perinatal literature identifies that abnormal fetal monitoring of various types may identify increased fetal risk. Table 3.2 reflects this literature as well as univariable analyses of the PIERS dataset for non-stress testing and maternal predictors of perinatal death or admission to NICU for >48 hours; other tests of fetal well-being were collected too infrequently to be considered. The biophysical profile is not listed because this test has not been demonstrated to be useful in women with hypertensive disorders of pregnancy or other high risk patients[37,93]; and, indeed may falsely reassure both practitioners and women when pregnancies are complicated by either early-onset IUGR[94] or pre-eclampsia[95]. Of fetal assessment modalities, umbilical artery Doppler studies are the best supported[37,96].

In 1153 women who participated in the Dutch Obstetric Consortium's HYPITAT trial at gestational ages $\geq 36^{+0}$ weeks[97], nulliparity, increasing body mass index (BMI), heavy dipstick proteinuria (≥3+), increasing serum uric acid and increasing serum creatinine were independent antenatal predictors of adverse neonatal outcomes of: 5-minute Apgar score <7, cord pH <7.05, or NICU admission[98].

The independent value, within a multivariable model, of various additional Doppler studies in assessing maternal and perinatal risks associated with a diagnosis of pre-eclampsia (not predicting that diagnosis) has yet to be assessed. Preliminary data suggest that uterine and ophthalmic artery Doppler may assist in risk stratification[99,100].

While conserved in the miniPIERS model (see below), proteinuria was not retained in the fullPIERS model developed in women with pre-eclampsia. However, like uric acid, proteinuria may be important to identify risk in women with the full spectrum of the hypertensive disorders of pregnancy, as women with 0.3 g/d of proteinuria had complication rates above those of women managed as outpatients (gestational hypertension and pre-existing hypertension), meriting closer surveillance and endorsing 0.3 g/d as an appropriate threshold for determining in-patient management[101], confirming previous studies[102]. Adverse perinatal outcomes were higher still in women with 0.5 g/d proteinuria, as observed in miniPIERS, below[47,101].

OTHER

In Canada, in 2014, a new category of 'other' was added to the classification system, to raise awareness that blood pressure that is not consistently elevated in the office setting and at home is associated with maternal and perinatal risks that appear to be intermediate between those of women with normal blood pressure and those with hypertension in the office and ambulatory or home settings.

'White coat' effect

'White coat' hypertension is seen when blood pressure is elevated in the office, but normal by ambulatory blood pressure monitoring (ABPM) or at home. (See Chapter 1 for numerical values.)

White coat effect in early pregnancy is common (approximately 30%), similar to estimates outside of pregnancy[103]. The limited literature suggests that there is a heightened risk of adverse maternal outcomes compared with normotensive pregnancy, but the risks are probably smaller than with pre-existing hypertension[104]. Of these women, 40% progress to gestational hypertension and 8% to pre-eclampsia.

ABPM has identified that approximately 30% of women with gestational hypertension demonstrate a white coat effect on their blood pressure, although estimates have been as high as 70% in the third trimester[31]. There is wide variability in the rates of associated maternal and perinatal complications, but many studies have identified risk that is intermediate between that of normotensive women and that of women with gestational hypertension[31].

Masked hypertension

'Masked' hypertension refers to blood pressure that is normal in the office but elevated by ABPM or at home. (See Chapter 1 for numerical values.)

Masked hypertension may be present in about 30% of women with pre-existing hypertension[103].

However, the associated perinatal risks are unknown. Outside pregnancy, cardiovascular risk associated with masked hypertension is similar to that associated with sustained hypertension.

Masked gestational hypertension was seen in 4–15% of women in prospective cohort studies; pregnancy outcomes were similar to those of women with sustained gestational hypertension[105,106]. This diagnosis could be considered (and ABPM or home blood pressure monitoring performed) if there are unexplained maternal or perinatal complications that are associated with the hypertensive disorder of pregnancy, but the usefulness of this approach has not been studied.

INVESTIGATIONS TO CLASSIFY THE HYPERTENSIVE DISORDERS OF PREGNANCY

Pre-existing hypertension

Women with pre-existing hypertension are most likely (>95%) to have essential hypertension, but secondary causes should be considered. A basic work-up has been suggested for women for whom suspicion of a secondary cause is low (see the annually updated Canadian Hypertension Education Program document for a more extensive discussion (https://www.hypertension.ca/en/chep)).

Conditions such as obesity, associated non-alcoholic steatohepatitis, or immune thrombocytopoenia may make interpretation of blood work for pre-eclampsia end-organ dysfunction difficult later in pregnancy. Consequently, it may be appropriate to conduct additional baseline testing in women with these conditions early in pregnancy.

Women with a strong clinical risk marker for pre-eclampsia should be considered for baseline proteinuria quantification (by spot protein : creatinine ratio or 24 h urine collection) given the insensitivity of dipstick proteinuria testing. A fasting blood glucose ≥7 mmol/l prior to pregnancy or ≥5.3 mmol/l in pregnancy should prompt appropriate investigation and subspecialty referral[107].

An abnormal P wave in lead V1 by electrocardiogram may increase the risk for gestational hypertension or pre-eclampsia[108].

In terms of imaging, echocardiography may be useful in selected women, such as those with known or suspected left ventricular dysfunction or heart failure (https://www.hypertension.ca/en/chep). Plasma lipids should not be measured routinely because both cholesterol and triglycerides increase physiologically during pregnancy and are not considered when making treatment decisions.

When pre-eclampsia is suspected

Pre-eclampsia may be a disease in evolution, with clinical manifestations unfolding in a serial fashion. When there is ongoing suspicion of pre-eclampsia, the nature and frequency of serial surveillance are unclear, but a change in clinical status for mother or fetus would be a reasonable indication for repeat testing. Pre-eclampsia imitators share manifestations with pre-eclampsia, but require different treatments (Table 3.3).

Maternal investigations

In addition to measurement of blood pressure, women with suspected pre-eclampsia should undergo blood and urine testing as outlined in Table 3.3[70]. This testing is designed to (1) detect end-organ involvement that increases the risk of adverse maternal and/or perinatal outcomes (e.g., elevated serum uric acid), (2) detect one of those adverse outcomes (e.g., acute renal failure), (3) evaluate the seriousness of the adverse outcome (e.g., haemoglobin in setting of placental abruption) (Table 3.2), or (4) explore important differential diagnoses (e.g., acute fatty liver of pregnancy or primary renal disease).

The maternal testing in Table 3.3 (alone or in combination) is of prognostic value once pre-eclampsia has been diagnosed, but its value for the purposes of diagnosis is based on expert opinion. Most abnormalities are not specific to pre-eclampsia, so the usefulness of the testing relies more on multiple (rather than single) abnormalities. In addition, as differentiating pre-eclampsia from gestational hypertension can be difficult, it is possible that maternal venous Doppler studies, particularly renal interlobar vein impedance index (RIVI), will assist in this regard, but initial findings require further validation[109,110]. Innovative methods such as brain mapping with electroencephalography and advanced retinal imaging have not been fully evaluated, but may assist in targeting magnesium sulphate therapy towards those women who would most benefit from it[111,112].

Table 3.3 Investigations to diagnose and monitor women with a hypertensive disorder of pregnancy (reproduced with permission from the SOGC)[60]

Investigations for diagnosis	*Description in women with pre-eclampsia*	*Description in women with other conditions*
Maternal testing		
Uterine testing		
Urinalysis (routine and microscopy with/without additional tests for proteinuria)	Proteinuria (as discussed under *Proteinuria*) 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 phenochromocytoma, hyperaldosteronism, thyrotoxicosis, coarctation of the aorta, and withdrawal syndromes
Oxygen saturation		
Pulse oximetry	SpO_2 <97% associated with a heightened risk of severe complications (including non-respiratory)	May be decreased in any cardiorespiratory complication (e.g., pulmonary embolism)
CBC and blood film		
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 thrombocytopoenia (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)
Tests of coagulation		
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
Fibrinogen	↔	↓ 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[106] but ADAMTS13 antibody should be absent

continued

Table 3.3 *continued*

Investigations for diagnosis	*Description in women with pre-eclampsia*	*Description in women with other conditions*
Serum chemistry		
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 thrombocytopoenia), AFLP (along with liver dysfunction)
Serum uric acid	↑ associated wtih 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'† but to a lesser degree, and usually normal in TTP-HUS May be increased in other pregnancy-related conditions (e.g., intrahpatic 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 ↑ LDH/AST ratio (>22) with TTP-HUS[107]
Bilirubin	↑ unconjugated from haemolysis or conjugated from liver dysfunction	(early) ↑ in AFLP, ↑ with haemolytic anaemia, other liver disease with dysfunction, genetic diseases
Albumin	↓ associated with adverse maternal and perinatal outcomes	↓ as negative actue phase reactant with acute severe illness, malnutrition, nephrotic syndrome, crystalloid infusion
Fetal testing	Abnormalities are not specific to the cause of poor placentation and/or placental dysfunction	
Uterine artery Doppler velocimetry	Unilateral/bilateral notching, or elevated pulsatility index or resistance index may support a diagnosis of placental insufficiency including pre-eclampsia	

AFLP, acute fatty liver of pregnancy; APS, antiphospholipid syndrome; CBC, complete blood count; DIC, disseminated intravascular coagulation; HCTZ, hydrochlorthiazide; HUS, haemolytic-uraemic syndrome; ITP, immune thrombocytopoenic purpura; PET, pre-eclampsia; SpO_2, oxygen saturation by pule oximetry; RBC, red blood cell; TTP, thrombotic thrombocytopoenic purpura

The pre-eclampsia imitators are conditions with numerous manifestations shared by pre-eclampsia (Table 3.3)[46,113]. To greater or lesser degrees, all of these conditions share the clinical features of hypertension, central nervous system symptoms and abdominal pain, and the laboratory features of proteinuria, anaemia, thrombocytopoenia, micro-angiopathic haemolysis and elevated lactate dehydrogenase (LDH). However, acute fatty liver of pregnancy tends to have prominent vomiting, liver dysfunction (with jaundice and diabetes insipidus) and renal failure[114].

Thromboses and skin involvement suggest catastrophic antiphospholipid antibody syndrome[115]. Thrombotic thrombocytopaenic purpura-haemolytic uraemic syndrome (TTP-HUS) has prominent neurological manifestations (termed TTP), vomiting and renal manifestations (termed HUS); laboratory evidence of disseminated intravascular coagulation and elevated liver enzymes would be unusual[116]. Scleroderma renal crisis and malignant hypertension show predominant renal manifestations[117,118].

Phaeochromocytoma may mimic pre-eclampsia in both well-resourced and resource-limited settings[119,120], presenting as episodic headaches, anxiety (resembling a panic attack), altered skin sensation, seizures, flank pain, pallor, diaphoresis, tachycardia, paroxysmal hypertension with paradoxical orthostatic/postural hypotension (a fall in systolic blood pressure >20 mmHg or in diastolic blood pressure >10 mmHg upon standing), and

hyperglycaemia. Elevated plasma metanephrins, urinary catecholamines and imaging will secure the diagnosis.

The importance of determining whether or not pre-eclampsia (particularly in those exceptional cases with onset before 20 weeks or more than 3 days postpartum) may actually be another disorder is that subspecialty referral is warranted for specific therapy (beyond supportive care). Such specific therapies include immunosuppression and heparin for catastrophic antiphospholipid syndrome, plasma exchange and steroids for TTP-HUS, angiotensin converting enzyme (ACE) inhibitors for scleroderma renal crisis and alpha-agonists for phaeochromocytoma. Of course, women with acute fatty liver of pregnancy (AFLP) should be delivered immediately regardless of gestational age.

Biomarkers

Taking into account the points made above, in a minority of women with pre-eclampsia, clinical uncertainty around the diagnosis arises. It is in this context that translational biomarkers may improve diagnostic accuracy and clinical performance. Such women could be those who appear to have pre-eclampsia superimposed on pre-existing hypertension and/or renal disease[49–51], are highly symptomatic but normotensive and/or non-proteinuric, or present with either gestational hypertension or gestational proteinuria in isolation. These women with "atypical" pre-eclampsia bear the same risks as others with classically clinically defined disease[121]. Indeed, such women may bear increased risks as responses to their symptoms and signs may be delayed as they do not fulfil diagnostic criteria that can be strictly applied by clinicians unaware of the atypical presentation of pre-eclampsia in a significant subset of women.

As we approach the definition of varying phenotypes of pre-eclampsia (e.g., severe versus non-severe, early- versus late-onset) by clinical and biochemical criteria, adherence to standardised biomedical research protocols will hasten our understanding of the causes of pre-eclampsia and development of targeted treatment strategies. To assist in that process, the PRE-EMPT Global Pregnancy Collaboration (http://pre-empt.cfri.ca/colaboratory) has presented what they consider to be the minimum requirements for a data set in a study of pre-eclampsia that will facilitate comparisons[122]. In addition, they have presented a comprehensive or "optimal" data set for in-depth investigation of pathophysiology[122].

As intimated above, within the past decade, an imbalance between pro- and anti-angiogenic factors has been proposed to underlie many features of the maternal syndrome of pre-eclampsia[42,123–127]. While such an imbalance appears to be observed quite consistently in women with early-onset pre-eclampsia[41,43], it is shared with pregnancies complicated by placentally mediated fetal growth restriction[44]. Therefore, while angiogenic imbalance may reflect the presence of the underlying placental dysfunction particularly important with early-onset pre-eclampsia, it is unlikely to be a singular aetiological pathway but will be shared with risks of intrauterine growth retardation and fetal death[128,129].

In the near future, those biomarkers with the greatest potential to be introduced into day-to-day clinical care to individualise maternal and perinatal risk are PlGF and sFlt-1, either a single analyte (i.e., PlGF) or as a ratio between anti- and pro-angiogenic factors (e.g., sFlt-1/PlGF ratio)[41–43,45,123–127,130,131]. We are aware of two such platforms that are being licensed and brought to the international market.

The recently published PELICAN prospective multicentre study evaluated the diagnostic accuracy of low plasma PlGF concentration (<5th centile for gestation) in women presenting with suspected pre-eclampsia between 20^{+0} and 34^{+6} weeks' gestation (and up to 41 weeks' gestation as a secondary analysis)[45]. The outcome was delivery for confirmed pre-eclampsia within 14 days. Of 625 women, 346 (55%) developed confirmed pre-eclampsia. In 287 women enrolled $<35^{+0}$ weeks' gestation, PlGF <5th centile had high sensitivity (0.96; 95% confidence interval, 0.89–0.99) and negative predictive value (0.98; 0.93–0.995) for delivery for pre-eclampsia within 14 days; specificity was lower (0.55; 0.48–0.61). Area under the receiver-operating characteristic curve for low PlGF (0.87, standard error 0.03) for predicting delivery for pre-eclampsia within 14 days among women presenting with suspected pre-eclampsia was greater than all other commonly used tests, singly or in combination (range, 0.58–0.76; $p < 0.001$ for all comparisons). The authors concluded that PlGF is better than other currently used tests and presents an innovative

adjunct to management of such women. This is consistent with studies using the sFlt-1/PlGF ratio[125,126].

Adding Doppler studies may further improve the maternal and fetal risk stratification capacity of angiogenic imbalance in women with established pre-eclampsia[126,127].

Other time-of-disease potential biomarkers of both the presence of pre-eclampsia and its severity include neutrophil gelatinase-associated lipocalin (NGAL)[132–134], the marker of central nervous system injury S100B[135], leptin[136], interferon-γ[136] and glycosylated fibronectin[55].

Urinary tests of interest for the differentiation of pre-eclampsia from other hypertensive disorders of pregnancy are the Congo red test, podocyturia and kidney injury molecule-1[137–139]. (See Chapter 2 for further detail about the Congo red test.)

Fetal monitoring

Fetal testing is also listed in Table 3.3. Uterine artery Doppler velocimetry may be useful in hypertensive pregnant women to support a placental origin for the hypertension, proteinuria, and/or adverse conditions[140]; obstetric consultation would then be warranted.

Oligohydramnios, absent or reversed end-diastolic flow in the umbilical artery, or a deep, absent or reversed A wave in the ductus venosus would be more consistent with placental dysfunction than with decreased biological growth potential, uncertain dates, or aneuploidy as a cause of IUGR and may also be useful to inform timing of delivery[37,141–144]. Reduced maternal plasma PlGF implies IUGR of placental origin, rather than constitutionally small fetal size[44].

It is very important to note that the addition of biophysical profile to a schedule of fetal surveillance has not been shown to improve outcomes in high risk pregnancies[93]. Indeed, it appears that the biophysical profile tends to falsely reassure practitioners and lead to worse outcomes when pregnancies are complicated by either pre-eclampsia or IUGR[94,95].

THE PATIENT PERSPECTIVE

We support incorporating the patient perspective into care. Engaged patient advocacy organisations are the Preeclampsia Foundation (www.preeclampsia.org/), Action on Pre-eclampsia (APEC) (www.apec.org.uk/), Australian Action on Pre-eclampsia (AAPEC; www.aapec.org.au), New Zealand Action on Pre-eclampsia (NZ APEC) (www.nzapec.com/) and Association de Prevention et d'Actions contre la Pre-Eclampsie (APAPE) (www.eclampsie.moonfruit.fr/)[145].

The Preeclampsia Foundation advocates for better patient (and health care provider) education about the antenatal, early postnatal and long-term maternal implications of pre-eclampsia; an emphasis on early maternal signs and symptoms of pre-eclampsia; better doctor–patient communication about pre-eclampsia; and evidence-based guidelines for pre-eclampsia screening, detection; and management[145]. This is an approach that would seem to have global appeal, as illustrated by the following quote.

> ". . . they also have pre-eclampsia in the developed countries, but they don't die the way our own patients are dying, not because we do not know how to manage them but [because] they don't come early and by the time they come, it is so late".
>
> Focus Group Discussant, Society of Obstetricians and Gynaecologists of Nigeria, 03 Nov 2012

Post-traumatic stress

There is growing evidence that women may experience post-traumatic stress disorder up to 7 years postpartum[146–156], the prevalence of symptoms being highly variable, ranging from the minority to the majority of women, and higher after maternal hospitalisation for more than 1 week, preterm hypertensive disorder of pregnancy onset or delivery, NICU admission, adverse neonatal outcomes, or uncertainty about the child's long-term health[151]. Symptoms are not specific to the hypertensive disorders of pregnancy, and follow preterm delivery for other indications[155]. Although post-traumatic stress symptoms do not have an impact on infant cognitive or psychomotor development at 1 year of age, maternal symptoms are amenable to clinical psychological therapy, and earlier referral may abbreviate treatment[152].

Women and their maternity care providers seem to view experiences of pre-eclampsia differently. For health care professionals, pre-eclampsia represented the care that must be delivered, primarily responding to the biology of

pre-eclampsia. For women, generally lacking knowledge and understanding about pre-eclampsia, pre-eclampsia represents fear and risk[157].

Patient education and engagement

In a survey of women who had experienced pre-eclampsia, eclampsia and/or HELLP, pre-eclampsia was viewed as very important to all, and traumatic to many, respondents including 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[157].

Even in well-resourced settings, women are not knowledgeable about the hypertensive disorders of pregnancy, even those with pre-existing hypertension. They have a poor understanding of pre-eclampsia[158,159], and hypertensive disorders of pregnancy, even those with pre-existing hypertension, and are not satisfied with the medical information they receive. This suggests that clinicians should both place more value on informing women about either their condition or its potential course, and check that women have understood the information[160,161]. Although limited health literacy may complicate risk, communication tools have been developed for such purposes[160,161].

Current ANC practice guidelines offer little information on educating patients about pre-eclampsia. However, when women receive and understand education about pre-eclampsia, they are more likely to promptly report symptoms[159]. Formal study is required to see whether this will indeed lead to early diagnosis and management, and improved maternal and perinatal outcomes, as hoped[158,159].

Women enjoy participating in aspects of their care, be it receiving information as study participants[162], or participating in management of their blood pressure[163]. Women have expressed a preference for home or day care[164] and self (rather than 24-h ambulatory) blood pressure monitoring[165]. They do not object to being randomised[166].

BEST PRACTICE POINTS

(Please see Appendix 3.1 for the evaluation of the strength of the recommendation and the quality of the evidence on which they are based.)

1. Hypertensive disorders of pregnancy should be classified as pre-existing hypertension or gestational hypertension with or without pre-eclampsia, or 'other' hypertension on the basis of different diagnostic and therapeutic considerations.
2. The presence or absence of pre-eclampsia must be ascertained, given its clear association with more adverse maternal and perinatal outcomes.
3. In women with pre-existing hypertension, pre-eclampsia should be defined as resistant hypertension, new *or* worsening proteinuria, one or more adverse conditions, or one or more severe complications.
4. In women with gestational hypertension, pre-eclampsia should be defined as new-onset proteinuria, one or more adverse conditions, or one or more severe complications.
5. The assessment of maternal angiogenic factor balance appears to inform the diagnosis of pre-eclampsia, and other placental complications of pregnancy, where uncertainty exists, especially when 'superimposed pre-eclampsia' is suspected.
6. Severe pre-eclampsia should be defined as pre-eclampsia complicated by one or more severe complications.
7. For women with pre-existing hypertension, serum creatinine, fasting blood glucose, serum potassium and urinalysis should be performed in early pregnancy if not previously documented.
8. Among women with pre-existing hypertension or those with a strong clinical risk marker for pre-eclampsia, additional baseline laboratory testing may be based on other considerations deemed important by health care providers.
9. Women with suspected pre-eclampsia should undergo laboratory maternal testing and a schedule of pertinent fetal testing described in Table 3.3.

10. 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), and for timing of delivery.
11. The biophysical profile is not recommended as part of a schedule of fetal testing in women with a hypertensive disorder of pregnancy.
12. If initial testing is reassuring, maternal and fetal testing should be repeated if there is ongoing concern about pre-eclampsia (e.g., change in maternal and/or fetal condition).
13. In resource-constrained settings, the miniPIERS model can provide personalised risk estimation for women with any hypertensive disorder of pregnancy. In many of these women, the ultimate diagnosis cannot be confirmed until at least 3 months after delivery.
14. Health care providers should be alert to symptoms of post-traumatic stress following a hypertensive disorder of pregnancy; and refer women for appropriate evaluation and treatment.
15. 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.
16. Information should be re-emphasised at subsequent visits.

PRIORITIES FOR UNDER-RESOURCED SETTINGS

Hypertensive disorders of pregnancy diagnosis and severity

Identifying women with pregnancy hypertension before it becomes life-threatening is particularly important for colleagues in resource-constrained settings. For example, in a single-site retrospective analysis of demographic and clinical data of 1027 patients with eclampsia over a 10-year period, Adamu *et al*. observed a maternal case fatality rate of 17.9%, which was particularly high among women who had received no antenatal care (18.7%), compared with those who had received such care (5.9%)[167]. In this series, the perinatal mortality rate was 38%, of which 81% were stillbirths.

For many colleagues in the global maternal care community, access to laboratory facilities and modalities for outpatient blood pressure monitoring is limited or even absent. Therefore, it has been imperative to determine how best to classify pregnancy hypertension in resource-constrained settings. Clarifying the diagnosis of pre-eclampsia is a clinical priority as the WHO Multicountry Survey on Maternal and Newborn Health has determined that maternal near-miss cases were eight times more frequent in women with pre-eclampsia, and up to 60 times more frequent in women with eclampsia, when compared with women with other hypertensive disorders of pregnancy[168].

It is imperative that all women everywhere have access to accurate blood pressure measurements and dipstick proteinuria assessment as a global priority. In the UK, which had maternal mortality data a century ago that were similar to those of many less-developed countries today, over 90% of the observed reduction in maternal mortality occurred prior to the provision of either effective antihypertensives or magnesium sulphate (Figure 3.2). As stated above, the provision of antenatal care including blood pressure and proteinuria assessment, with appropriate referral pathways, has been associated with markedly reduced maternal mortality in Sri Lanka, even during the period when care was complicated by the presence of civil war[3] (Figure 3.3). (See Chapters 1 and 2 for priority recommendations for further detail about accurate and cost-effective semi-automated blood pressure devices and costs of proteinuria detection, as well as advocacy tools for colleagues to use to elicit appropriate funding for these key resources for pregnant women wherever they reside[169,170]).

In many less-developed countries, women do not present for maternity care until at least 20 weeks' gestation[171–182]. As a result, the firm classification of a hypertensive disorder of pregnancy may not be achievable until after the woman has delivered. In response to this reality, we have developed and validated the miniPIERS model to personalise the risk for severe complications experienced by women with any hypertensive disorder of pregnancy who present in under-resourced settings[48]. Data were collected

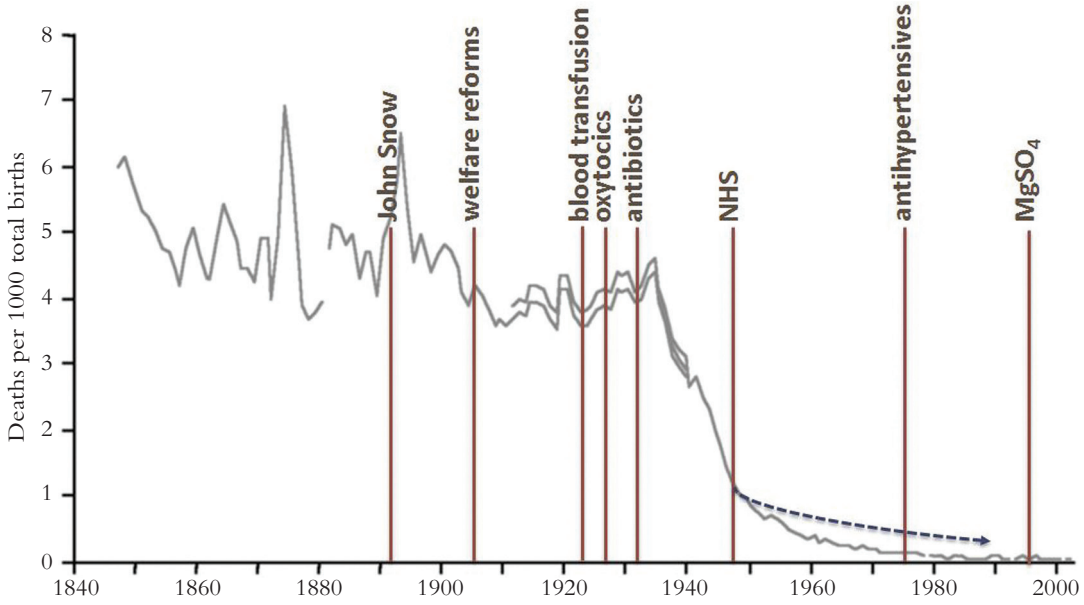

Figure 3.2 The rate of maternal deaths in the UK compared with sentinel events in maternity care and public health. The dotted line represents the projected rate of fall without the introduction of universal pregnancy and postpartum care through the National Health Service

prospectively on 2081 women with any hypertensive disorder of pregnancy admitted to a participating centre in Brazil, Fiji, Pakistan, South Africa, or Uganda. The final miniPIERS model includes parity (nulliparous versus multiparous); gestational age on admission (as best ascertained at the time of the encounter), headache/visual disturbances, chest pain/dyspnoea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria. In the miniPIERS cohort, up to 40% of the women were unbooked at the time that their hypertension was first diagnosed. However, best estimation of gestational age at that encounter led to gestational age being a powerful and independent identifier of maternal risk in the miniPIERS cohort.

An online calculator (cfri.ca/piers) is available for entry of continuous variables (such as gestational age) into the miniPIERS model to provide real-time personalised risks to all women whose caregivers have access to the internet. An mHealth app is in development and will be made available through the PRE-EMPT website (pre-empt.cfri.ca).

Once women in less-resourced settings are diagnosed with pre-eclampsia every effort should be made to give them access to oximetry and appropriately targeted laboratory testing[47].

Over 90% of women who suffer hepatic haematoma and/or rupture will have preceding HELLP syndrome[183].

Defining a woman with 'severe' pre-eclampsia as one with a miniPIERS predicted probability >25% classifies women with 85.5% accuracy; this accuracy is greater if pulse oximetry is added to the model[184]. We believe that miniPIERS could be used in resource-constrained settings to identify women who would benefit most from interventions such as magnesium sulphate, antihypertensives, or transportation to a higher level of care, especially if supported by a usability-tested mobile health (mHealth) application such as PIERS on the Move[185,186].

Facility versus community

In our view, maternity care providers should be able to screen women for pre-eclampsia and the other hypertensive disorders of pregnancy irrespective of where that woman is encountered. In addition, should hypertension be detected, then personalised risk assessment should be universal through the strengths and flexibility of mHealth. In the community, the determination of an individual woman's hypertensive disorder of pregnancy will

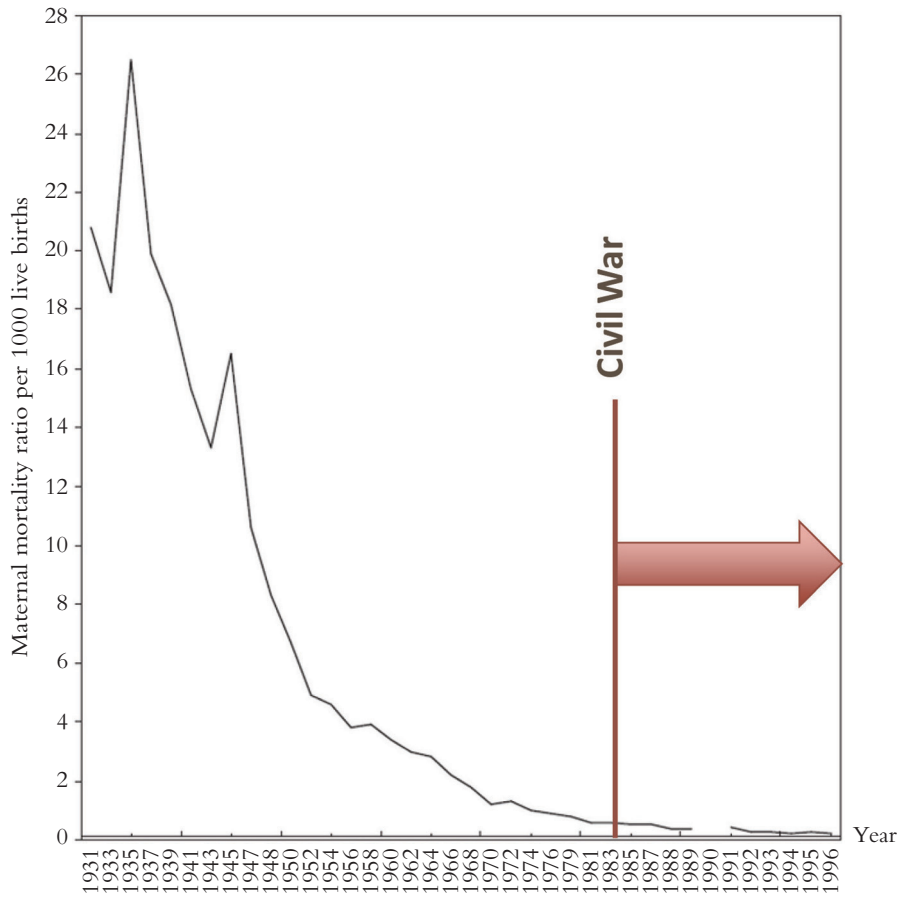

Figure 3.3 The trend of the maternal mortality ratio in Sri Lanka, 1931–1996 (modified from Fernando *et al.*[3])

be driven largely by the presence or absence of proteinuria and knowledge of any prior diagnosis of hypertension.

With the miniPIERS model and app, especially supplemented by oximetry, maternity care providers can assess and triage risk for hypertensive women wherever they are, whether that is in a hut in sub-Saharan Africa or in a private practice on Harley Street[48,184–186]. The outpatient use of a point-of-care assessment of angiogenic factor imbalance and GlyFn may aid in decision-making about the necessity for, and timing of, admission[45,55,126].

Where resources are limited, miniPIERS-based maternal assessment may remain the cornerstone of care either out-of-hospital/heath centre or in facilities where laboratory support is not readily accessible. However, the certainty of discriminating between pre-eclampsia and other hypertensive disorders of pregnancy is increased by access to laboratory results and ancillary clinical investigations, so practitioners who have the advantage of working in well-resourced settings should use evidence-based assessment of risk that takes into account maternal demographics, symptoms, signs, fetal assessment, and laboratory tests. Using the fullPIERS model limits the scope, and cost, of that testing for maternal risk assessment[47].

Finally, there is a need to strengthen pre-eclampsia knowledge among women and their communities, as illustrated by the following quote and discussed above.

> "We arrange community based meetings to educate the women, their family members and traditional birth attendants. We try to share knowledge with them about pregnancy, and complications during pregnancy, so much so, that we can prevent women from dying."
>
> Lady Health Supervisor, Matiari, Pakistan, 19 Mar 2012

WHAT INTERNATIONAL GUIDELINES SAY

We have compared the recent international guidelines in English, French, Dutch and German[58]. Included in this review were the guidelines developed in: Canada (Society of Obstetricians and Gynaecologists of Canada (SOGC) (2014), Association of Ontario Midwives (AOM))[60,187,188]; the United Kingdom (National Institute for Health and Clinical Excellence (NICE), Pre-eclampsia Community Guideline (PRECOG), PRECOG II)[59,189,190]; the United States of America (American College of Obstetricians and Gynecologists (ACOG), American Society of Hypertension (ASH))[62,191] and New Zealand (Society of Obstetric Medicine of Australia and New Zealand (SOMANZ))[192]; Australia (Queensland Maternity and Neonatal Clinical Guidelines Program (QLD))[193,194]; The Netherlands (Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG))[195]; and Germany (Deutschen Gesellschaft fur Gynakologie und Geburtshilfe (DGGG))[196]. Most clinical practice guidelines (CPGs) were national (8/13), but three were multinational, from Australasia (Society of Obstetric Medicine of Australia and New Zealand (SOMANZ))[197], the World Health Organization (WHO)[198,199], and the European guideline for cardiovascular diseases (ESC)[200].

We determined that there is between-guideline consistency with regards to the definitions of chronic (pre-existing) and gestational hypertension (Appendix 3.2). Chronic hypertension pre-dates pregnancy or is documented before 20 weeks. One guideline specifies that this must be essential (i.e., without known cause (QLD)) and three list either secondary causes and/or comorbid conditions that would influence decisions about blood pressure control (AOM, QLD, SOGC).

By general consensus, gestational hypertension is new hypertension that develops at or after 20 weeks; although implied by all guidelines, some specify that there must be neither proteinuria (QLD) nor other features of pre-eclampsia (N = 2) (ACOG, NICE). Three guidelines specify that blood pressure must return to normal postpartum, at 12 weeks (N = 2) (QLD, NVOG) or at an unspecified time (ACOG).

All guidelines define pre-eclampsia as gestational hypertension with proteinuria. More often than not, this is a mandatory criterion (N = 5) (PRECOG, PRECOG II, WHO, NICE, NVOG) (compared with not mandatory (N = 4) (AOM, QLD ACOG, SOGC)) (Appendix 3.3). Two CPGs specify that the proteinuria must resolve after delivery (PRECOG, PRECOG II). Although four also include gestational hypertension with one/more systemic feature of pre-eclampsia, there is no consistency with regards to those features that include fetoplacental abnormalities and/or maternal symptoms, signs and abnormal laboratory findings (ACOG, AOM, QLD, SOGC). The most common maternal manifestations listed are headache/visual symptoms (N = 4 CPGs), right upper quadrant/epigastric abdominal pain (N = 3), severe hypertension (N = 2), eclampsia (N = 2), pulmonary oedema (N = 3), low platelets (N = 4), elevated serum creatinine (N = 4), and elevated liver enzymes (N = 4); only one CPG specifies hyperreflexia. Fetal manifestations of pre-eclampsia are specified by three CPGs, all of which list IUGR (not defined) (N = 3) and abruption without evidence of fetal compromise (N = 3); one specifies stillbirth.

'Superimposed' pre-eclampsia is not clearly defined. Three CPGs do not address this at all, and six define it variably as worsening hypertension (N = 3) (AOM, ACOG, SOGC), new/worsening proteinuria (N = 3) (AOM, ACOG, SOGC) or one/more other systemic features (N = 4) (NVOG, AOM, ACOG, SOGC). 'Worsening' hypertension is defined clearly by two CPGs as either: (1) a sudden increase in blood pressure or the need to increase antihypertensive dose (ACOG), or (2) the need for three antihypertensive medications for blood pressure control at ≥20 weeks (SOGC). Proteinuria is a mandatory criterion according to ACOG (Appendix 3.3).

'Severe' pre-eclampsia is defined by most (7/9) CPGs, but there is little consistency. Heavy proteinuria is included by some (N = 3) (WHO, NVOG, AOM), but specifically excluded by others (N = 2) (ACOG, SOGC). Five CPGs define end-organ complications of severe pre-eclampsia; the most common maternal are: headache/visual symptoms (N = 5 CPGs), right upper quadrant/epigastric abdominal pain (N = 4), severe hypertension (N = 5), eclampsia (N = 2), pulmonary oedema (N = 3), low platelets (N = 4), renal insufficiency (N = 3), and elevated liver enzymes (N = 3); these mirror the diagnostic criteria used in

some guidelines. Fetal manifestations of pre-eclampsia are specified by three CPGs, all of which list stillbirth and none of which specify abruption without evidence of fetal compromise; IUGR is included by WHO and SOGC, but specifically excluded by ACOG. The SOGC 'severity' criteria are indications for delivery, and include some features that are in other CPGs: (1) define pre-eclampsia but not severe pre-eclampsia (e.g., stroke), (2) define both pre-eclampsia and severe pre-eclampsia (e.g., eclampsia, pulmonary oedema, platelet count $<100\times10^9$/L, and acute kidney injury), or (3) define neither pre-eclampsia nor severe pre-eclampsia but are widely regarded as indications for delivery (e.g., uncontrolled severe hypertension).

In the three CPGs that specify that proteinuria is mandatory to define pre-eclampsia (WHO, NICE, NVOG), severe pre-eclampsia is the development of: (1) pre-eclampsia at <34 weeks (WHO), or (2) one/more features of end-organ dysfunction that is either not defined (WHO, NICE) or listed as "symptoms" (NVOG), heavy proteinuria (NVOG, WHO), or severe hypertension (NVOG, WHO) (Appendix 3.3).

In the four CPGs that do not include proteinuria as mandatory to define pre-eclampsia (AOM, QLD ACOG, SOGC), severe pre-eclampsia is the development of: (1) pre-eclampsia at 34 weeks (AOM), (2) proteinuria plus one/more features that alone would signify pre-eclampsia (cerebral/visual disturbances, pulmonary oedema, platelet count, 100×10^9/L, renal insufficiency, or elevated liver enzymes) (ACOG), or (3) one/more features of end-organ dysfunction described as: heavy proteinuria (AOM), one/more features of HELLP (QLD), new persistent and otherwise unexplained right upper quadrant/epigastric abdominal pain (ACOG), severe hypertension (AOM, ACOG), or those dysfunctions requiring delivery (SOGC) (Appendix 3.3).

Eclampsia is consistently defined by new onset and otherwise unexplained seizures in the setting of pre-eclampsia (N = 5 CPGs) (NICE, QLD, WHO, ACOG, SOGC). No guideline defines the widely used term, 'imminent eclampsia.'

PRIORITIES FOR FUTURE RESEARCH

All future research activities should be compliant with new international, consensus-derived minimal standards for pre-eclampsia research[122]. Through the PRE-EMPT Global Pregnancy Collaboration, investigators will be able to gain access to data management platforms by the end of 2016 (https://pre-empt.cfri.ca/colaboratory). It is a global imperative that representative biobanks are developed that have whole blood, plasma, serum, placental tissue to inform our understanding of pathways to healthy and complicated pregnancies, and the design of tailored interventions, for the most vulnerable women in less developed countries.

Biomarkers and biology

In our opinion, a singular priority is to better determine the biomarkers that are either specific to pre-eclampsia or more general to placental disease and are relevant to women in specific global regions. How these variations in the pathways towards, and responses to, disease modify the performance of current, translational and future diagnostic and classification tests is largely unknown.

Through better understanding of the biology of pre-eclampsia and the other hypertensive disorders of pregnancy, we will be enabled to better define and sub-classify the forms of hypertensive disorders of pregnancy that complicate pregnancies globally[41]. It is almost certain that the pathways to gestational hypertension and pre-eclampsia vary between women in well-resourced, more socially liberal countries, and those from less-resourced and more socially conservative countries. While the clinical manifestations of the disease appear to be common between communities of women, we need to determine whether the pathways to disease are shared. Differential origins of disease may arise due to variability in the social, environmental, infectious, and inflammatory determinants of maternal health and vulnerability.

The interaction between genes, the epigenome, commensal and pathological organisms, and the wider environment must vary between and within clusters of women. Indeed, biomarkers passed over in more-developed countries may become important time-of-disease risk identifiers in less-developed countries where the burden of severe disease with multiple end-organ complications is far greater. Such a biomarker is S100B[135].

Obtaining robust socio-demographic, clinical and biomarker data from before pregnancy, during

pregnancy (normal and complicated), and at time of disease is an urgent priority, especially for women in less-developed countries who bear a disproportionate burden of risk in terms of the development of pre-eclampsia, from dying from it, or losing their baby to it.

Precision medicine

For better assessment of personalised risks borne by women with a hypertensive disorder of pregnancy, we need to strengthen the miniPIERS model with pulse oximetry[48,184] and/or point-of-care assessment of angiogenic factor balance and GlyFn[42,43,45,55], should they be shown to improve the performance of the miniPIERS model. This may place advanced diagnostic capability in the hands of minimally trained, mHealth app-supported health workers in women's homes.

The incremental value of supplementing and/or recalibrating the fullPIERS model with angiogenic factors (e.g., PlGF) and/or GlyFn needs to be assessed. In addition, expanding the scope of fullPIERS to include women with all hypertensive disorders of pregnancy would improve its clinical utility. Recalibration of the model may well be required.

Similar parallel models to miniPIERS and fullPIERS are required to assess fetal risks and to optimise the timing of delivery and long-term outcomes for the fetuses of pregnancies complicated by pregnancy hypertension. Initially, this research is likely to be focused on well-resourced settings and, subsequently, on less-resourced settings. However, it must be remembered that there are many highly resourced centres providing care in less-developed countries. Partnering with such institutions will accelerate discovery that is pertinent to the global maternal population.

Markers of maternal cardiorespiratory health

A priority for research is the better assessment of the cardiorespiratory status of pregnant women, especially those with pre-eclampsia.

A prospective population-based study with nested case–control analysis used the UK Obstetric Surveillance System to identify all 25 women in the UK over a 6 year period with myocardial infarction (MI) in pregnancy, compared with a control group of 1360 women. Following mutivariable logistic regression, hypertension and pre-eclampsia were independently associated with MI in pregnancy as well as maternal age, smoking and twin pregnancy[201]. This may stem from global diastolic dysfunction, left ventricular remodelling, interstitial pulmonary fluid and increased brain natriuretic peptide (BNP) that may represent an adaptive response to maintain myocardial contractility with pre-eclampsia, at least at term in less- and more-developed settings[202–205]. These preliminary findings are consistent with what has been observed in the miniPIERS and fullPIERS studies with respect to pulse oximetry[47,76,184].

These findings need to be confirmed and expanded across the clinical spectrum of disease (early- and late-onset pre-eclampsia) as well as the geographical and socio-economic spectra in which pregnant women find themselves.

The impact of classification

Finally, implementation research observing the impact on maternal and perinatal outcomes and health services costs (direct and indirect) of introducing new classification paradigms is important, so that health decision-makers can make evidence-informed choices about defining national classification systems. Such implementation research might usefully include a stepped wedge design through a series of jurisdictions.

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