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HYPERTENSIVE EMERGENCIES (BM BAUMANN, SECTION EDITOR)

Pre-eclampsia: An Update

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Abstract Pre-eclampsia remains the second leading direct cause of maternal death, >99 % of which occurs in less developed countries. Over 90 percent of the observed reduction in pre-eclampsia-related maternal deaths in the UK (1952–2008) occurred with antenatal surveillance and timed delivery. In this review, we discuss the pathogenesis, diagnostic criteria, disease prediction models, prevention and management of pre-eclampsia. The Pre-eclampsia Integrated Estimate of RiSk (PIERS) models and markers of angiogenic imbalance identify women at incremental risk for severe pre-eclampsia complications. For women at high risk of developing pre-eclampsia, low doses of aspirin (especially if started <17 weeks) and calcium are evidence-based preventative strategies; heparin is less so. Severe hypertension must be treated and the Control of Hypertension In Pregnancy (CHIPS) Trial (reporting: 2014) will guide non-severe hypertension management. Magnesium sulfate prevents and treats eclampsia; there is insufficient evidence to support alternative regimens. Pre-eclampsia predicts later cardiovascular disease; however, at this time we do not know what to do about it.

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Introduction

Pre-eclampsia, classically defined as proteinuric gestational hypertension [1], remains the second leading cause of direct maternal mortality, accounting for some 70–80,000 maternal and 500,000 perinatal deaths globally annually [2]. Over 99 % of these foreshortened lives are lost in less developed countries, primarily in South Asia and sub-Saharan Africa [2]. This report will focus on important developments over the past 3 years as they relate to our understanding of the origins, management and consequences of pre-eclampsia.

Classification

Generally, pre-eclampsia has been classified as either 'mild' or 'severe' and within the context of broader classification systems for the hypertensive disorders of pregnancy (HDP). Most recently, such classification systems have been published by the National Institute for Health and Clinical Excellence (NICE) [3], the World Health Organization (WHO) [4], the American College of Obstetricians and Gynecologists (ACOG) [5], the International Society for the Study of Hypertension in Pregnancy (ISSHP) [6] and the Society of Obstetricians and Gynaecologists of Canada (SOGC) (published in brief and in full) [7••, 8••].

While much of each classification system is in common, with a general broadening of definitions of pre-eclampsia to include criteria beyond solely proteinuric gestational hypertension, the newly published Canadian guideline has added greater clarity to issues around white coat and masked hypertension (Table 1). More importantly, SOGC limits the definition of 'severe' pre-eclampsia to criteria that mandate delivery of women currently pregnant and includes an intermediate group of criteria that requires increased surveillance short of delivery ('adverse conditions') (Table 2). This is not to say that women with non-severe pre-eclampsia may not also require delivery.

This approach is unique, as it does not mix criteria that mandate increased surveillance with those that mandate delivery, as do other classification systems. The SOGC paradigm has used the international miniPIERS [9•] and fullPIERS [10] (Pre-eclampsia Integrated Estimate of RiSk) projects to establish objective criteria, as other classification systems' severity criteria fail to stratify risk accurately in women with pre-eclampsia [11]. Our hope is that the new SOGC classification criteria will more clearly guide decision making related to expectant management and the timing of delivery in women who present with pre-eclampsia at all gestational ages. This may be most useful in low volume and rural and remote settings where practitioners have less experience dealing with the condition.

Pathogenesis and Prediction of Pre-eclampsia

Pre-eclampsia is a clinical phenotype reflecting a multisystem disorder, the origins of which lie in interactions between the mother's condition both prior to and in early pregnancy and the fetoplacental unit. Those women developing early onset preeclampsia predominately do so in response to inadequate placentation (so-called 'placental pre-eclampsia,' generally associated with fetal growth restriction), while those developing pre-eclampsia at or near term predominately do so as a

Table 1 Classification of the hypertensive disorders of pregnancy [7••, 8••]

	Comments
Pre-existing (chronic) hypertension	This is defined as hypertension that is present either pre-pregnancy or that develops at <20° 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 pre-eclampsia	This is also known 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 ≥20° 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 pre-eclampsia	Evidence of pre-eclampsia may appear only many weeks after the onset of gestational hypertension. Pre-eclampsia is defined by gestational hypertension 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)
Pre-eclampsia	Pre-eclampsia may arise de novo. It is defined by gestational hypertension 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 complications‡
'Other hypertensive effects' *	
Transient hypertensive effect	Elevated BP may be due to environmental stimuli or the pain of labor, 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. *These may occur in women whose BP is elevated at $<20^{+0}$ or $\geq 20^{+0}$ weeks are suspected of having pre-existing or gestational hypertension/preeclampsia, respectively. ¥Please see Table 2 for definitions of adverse conditions and severe complications of pre-eclampsia

Table 2 Adverse conditions and severe complications [7••, 8••]

Organ system affected	Adverse conditions (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/dyspnea	• Uncontrolled severe hypertension (over a period of 12 h despite use of three antihypertensive agents),
	• Oxygen saturation <97 %	• Oxygen saturation <90 %, need for ≥50 % oxygen for >1 h, intubation (other than for cesarean section), pulmonary edema
		• Positive inotropic support
		• Myocardial ischemia or infarction
Hematological	• Elevated WBC count	• Platelet count $<50\times10^9$/l
	• Elevated INR or aPTT • Low platelet count	• Transfusion of any blood product
Renal	• Elevated serum creatinine	• Acute kidney injury (creatinine >150 μM with no prior renal disease)
	• Elevated serum uric acid	• New indication for dialysis
Hepatic	• Nausea or vomiting	• Hepatic dysfunction (INR >2 in absence of DIC or warfarin)
	• RUQ or epigastric pain • Elevated serum AST, ALT, LDH, or bilirubin	• Hepatic hematoma or rupture
	• Low plasma albumin	
Feto-placental	• Non-reassuring FHR	• Abruption with evidence of maternal or fetal compromise
	• IUGR	• Reverse ductus venosus A wave
	• Oligohydramnios • Absent or reversed end-diastolic flow by Doppler velocimetry	• 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 ischemic neurological deficit <48 h, *RUQ* right upper quadrant, *TIA* transient ischemic attack

result of pre-existing maternal conditions (so-called 'maternal pre-eclampsia') [12, 13]. Clearly, there will be women who will develop a blended form of pre-eclampsia on the basis of both placental and maternal factors [12].

Recent activity in this field has involved multivariable models predictive of the later development of pre-eclampsia. These models incorporate a variety of clinical, ultrasound and biochemical variables, are thought-provoking, but fall short of criteria making them ready for clinical use. An angiogenic imbalance [excessive soluble fms-like tyrosine kinase (sFlt)-1 or endoglin; reduced free placental growth factor (PlGF)] has been proposed to underlie many, if not most, cases of pre-eclampsia [14, 15]. This may well be true for early onset pre-eclampsia (with onset before 34^{+0} weeks) [16••]. However, the more common pathway to disease is based on maternal factors that lead to a biological susceptibility to pre-eclampsia, the majority of which arises at term [2].

There is a recent proposal that pre-eclampsia could usefully be redefined and subclassified on the basis of biomarkers reflecting placental (vs. maternal) pre-eclampsia [17•]. While we have data that support the role of PlGF in identifying women with pre-eclampsia, this marker of imbalance was similarly reduced in women whose pregnancies were complicated by normotensive fetal growth restriction of placental origin, but not in women whose fetuses were constitutionally small [18, 19•].

Multiple screening tests for pre-eclampsia have been proposed, but are all limited by somewhat low areas under the receiver-operating characteristic curve (AUC ROC). For example, Myatt et al. have proposed a screening test for pre-eclampsia for use in low-risk nulliparous women that includes African American race, systolic blood pressure, body mass index (BMI), education level, a disintegrin and metalloproteinase domain-containing protein (ADAM)-12, pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF), which yielded an AUC ROC of 0.73 [95 % confidence interval (CI) 0.69-0.77] [20].

The international Screening for Pregnancy Endpoints (SCOPE) study also developed and validated models to predict pre-eclampsia in nulliparous women [21, 22••, 23]. In 3,572 "healthy" nulliparous women with a singleton pregnancy enrolled in SCOPE, clinical risk factors associated with an

increased risk for pre-eclampsia and identifiable at 14–16 weeks' gestation were maternal age, mean arterial blood pressure, BMI, family history of pre-eclampsia, family history of coronary heart disease, maternal birth weight and vaginal bleeding for at least 5 days [24]. Factors associated with reduced risk for pre-eclampsia were a previous single miscarriage with the same partner, taking at least 12 months to conceive, high intake of fruit, cigarette smoking and alcohol use during the first trimester [24]. The AUC ROC, with internal validation, was 0.71 [standard error 0.002]; uterine artery Doppler indices did not improve performance (AUC ROC 0.71 [SE 0.003]). In predicting preterm pre-eclampsia, this model achieved an AUC ROC of 0.76 [95 % CI 0.67-0.84]; this model could be improved to produce an AUC of 0.84 [95 % CI 0.77-0.91] with the addition of PlGF (but not other angiogenic factor) measurement [22••]. However, neither model is robust enough to warrant introduction into clinical practice.

Within SCOPE, and using a metabolomics approach, Kenny et al. identified a largely dyslipidemic metabolic profile that was predictive of term pre-eclampsia [21], supportive of the concept of maternal pre-eclampsia predominating with term disease. In parallel, with proteomic analysis of blood, urine and amniotic fluid, a number of pilot studies have identified a variety of proteomic profiles worth further study [25–30]. Building on these data, the European IMPROvED Consortium aims to recruit 5,000 low-risk nulliparous women to assess and refine metabolomics- and proteomics-based tests from blood samples obtained at 15 and 20 weeks' gestation, with optional testing and biobanking at 11 and 34 weeks [31].

Prevention of Pre-eclampsia

Heparin

The evidence for the use of either unfractionated or low-molecular-weight heparin (LMWH) is mixed and based on a number of small trials administering heparin to pregnant women with a history of various placental complications in previous pregnancies. The 2013 Cochrane review found that prophylactic doses of heparin (of any type) versus no treatment decreased perinatal mortality (RR 0.40 [95 % CI 0.20-0.78]), delivery <34 weeks (RR 0.46 [95 % CI 0.29-0.73]) and small-for-gestational age (SGA) infants (RR 0.41 [95 % CI 0.27-0.61]) [32]. Focusing solely on LMWH, a second review found that LMWH versus no treatment reduced the risk of 'severe' or early onset pre-eclampsia (RR 0.16 [95 % CI 0.07-0.36]), delivery <37 weeks (RR 0.77 [95 % CI 0.62-0.96]) and SGA infants (RR 0.42 [95 % CI 0.29-0.59]) [33]. Both reviews revealed moderate heterogeneity between the informative trials [32, 33]. A recent international audit of the maternal and fetal safety of tinzaparin observed serious bleeding events (before, during and after delivery) *probably* related to tinzaparin in 2.3 % of pregnancies and *possibly* related to tinzaparin in 7.7 %. Currently, the UK NICE guideline development group considered that "there is currently insufficient evidence for considering that…[LMWH]…may prevent hypertensive disorders during pregnancy," especially when balanced against the risks associated with LMWH [3]. We concur.

Calcium 'Supplementation' Versus 'Replacement'

In areas where dietary calcium intake is low, calcium supplementation during pregnancy (at doses of 1.5-2.0 g elemental calcium/day) is broadly recommended, especially for those women at high risk of developing pre-eclampsia (RR 0.22 [95 % CI 0.12-0.42]) [4, 34]. However, on the basis of inconclusive evidence, there is concern that excessive calcium supplementation may be harmful. Calcium supplementation (but not dietary calcium) has been associated with increased myocardial infarction risk [35], while administration of 1.5 g calcium/day during pregnancy may cause rebound postnatal bone demineralization [36, 37•].

Therefore, might a lower dose of calcium (replacement to the recommended dietary allowance during pregnancy of 1–1.3 g/day) confer adequate benefit without the possible hazards of higher dose calcium supplementation? In a recent meta-analysis of trials of low-dose calcium (<1 g/day), with or without other supplements, pre-eclampsia was reduced consistently (RR 0.38 [95 % CI 0.28–0.52]), as well as for subgroups [38••]. In addition, the incidence of low birth weight (<2500 g) was reduced (RR 0.20 (95 % CI 0.05-0.88]).

Acetylsalicylic Acid

Low-dose acetylsalicylic acid (aspirin, 75 mg) is broadly recommended for the prevention of pre-eclampsia in women at 'high risk' of developing the condition (as defined in the relevant trials) [39, 40]. A secondary meta-analysis of the relevant trials suggests that low-dose aspirin should be initiated before 17 weeks of pregnancy [41]. When compared with controls, aspirin started at $\leq 16^{+6}$ weeks was associated with a significant reduction in 'severe' (as defined using 2002 ACOG criteria [42]) (RR 0.22 [95 % CI 0.08-0.57]) but not mild (RR 0.81 [95 % CI 0.33-1.96) pre-eclampsia. This analysis is potentially biased, but does encourage early use of aspirin pending risk stratification, as above.

Risk Stratification at Time of Disease

None of these approaches to the prevention of pre-eclampsia is likely to prevent a significant proportion of the burden of

disease. Therefore, we believe that the focus of current efforts should be directed toward timely diagnosis, risk stratification and evidence-based management. Notwithstanding parallel improvements in general conditions for women, in absolute numbers, data from the ongoing British Confidential Enquiries into Maternal Deaths show that the introduction of the National Health Service with free maternity care and, subsequently, ready access to reproductive choice through contraception and abortion services was associated with a rapid fall in the number of maternal deaths attributed to pre-eclampsia and eclampsia (Fig. 1). Pre-eclampsia- and eclampsia-related deaths have fallen by 90 %. However, it should be noted that over 90 % of that fall was achieved *prior* to the introduction of either effective antihypertensives for the management of the hypertension of pre-eclampsia [43, 44] or the use in the UK of magnesium sulfate ($MgSO_4$) for eclampsia and treatment following the Collaborative Eclampsia and Magpie Trials, respectively [45, 46]. Therefore, much of this report is focused on the somewhat arcane topics of pre-eclampsia diagnosis, risk stratification and timing of delivery.

Blood Pressure Measurement

Blood pressure measurement remains a cornerstone of the screening for, and diagnosis of, pre-eclampsia [3–6, 7••, 8••]. An important advance in the move toward community-level detection of pregnancy hypertension in less developed countries has been the development of the semi-automated Microlife BP 3AS1-2 sphygmomanometer®, which has been validated in women with the hypertension of pre-eclampsia [47•]. This device avoids the errors intrinsic in manual blood pressure measurement in pregnancy (especially terminal digit preference [48]), can be used by minimally trained community-level health-care providers and costs less than $25 USD per unit. There is a general movement toward automated blood pressure measurement, which will help address issues related to both white coat and masked hypertension [49].

Urine Protein Measurement

The obstetric gold standard of 24-h urine collection is frequently inaccurate and not a precise measure of either proteinuria or creatinine clearance [50]. Additionally, a recent systematic review of the spot protein:creatinine (PrCr) and albumin:creatinine (ACR) ratios as diagnostic tests for significant proteinuria (compared with the 24-h collection) in hypertensive pregnant women determined that the spot PrCr ratio (cutoff point of 30 mg/mmol) is a reasonable "rule-out" test for detecting significant proteinuria of 0.3 g/day or more in hypertensive pregnancy [51•].

Practitioners using either 24-h collections and/or the PrCr ratio in pregnancy must be particularly aware of the interaction between the protein estimation method and urinary concentration, as the pyrocatechol violet-dye method is vulnerable to overestimating urinary protein in dilute urine [52•].

Information related to the use of the ACR in pregnant women remains insufficient to guide practice [51•]. In pregnancy, urine is often dilute, and we found that almost 25 % of ACR results are clinically uninformative given that half of the

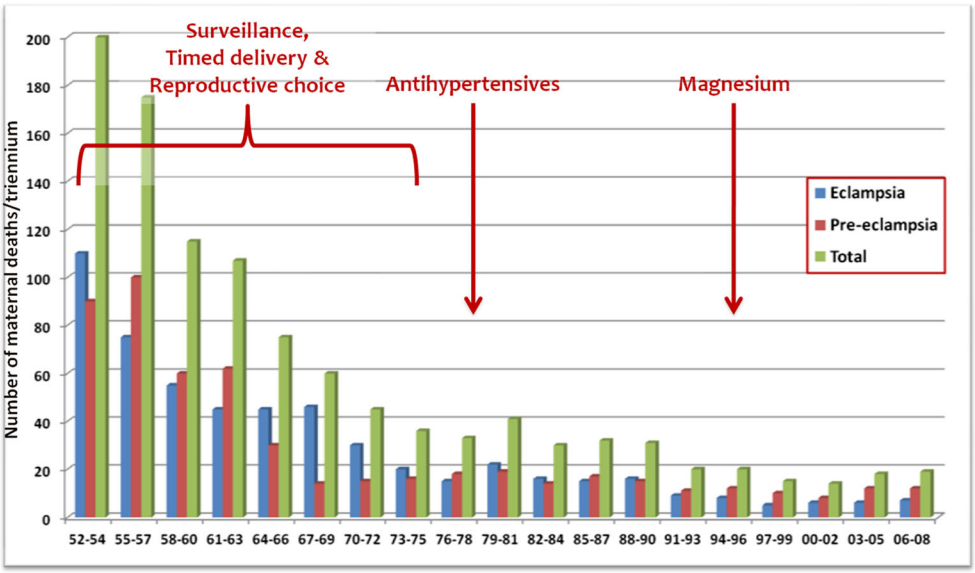

Fig. 1 The change in pre-eclampsia- and eclampsia-related maternal deaths in the UK (1952–2008). In absolute numbers, the number of these maternal deaths has fallen by 90 % per Confidential Enquiries into Maternal Deaths triennium since the first report. It should be noted that 90 % of that reduction occurred prior to the introduction of either effective antihypertensives or $MgSO_4$, during an epoch of improved (and free at point of care) maternity care (with resultant improved surveillance), timed delivery prior to the evolution to life-ending disease and reproductive choice (effective contraception and safe abortion services) to expand coitarche-to-pregnancy and interpregnancy intervals

samples have urinary albumin levels below the assay detection limit and half have no measurable albuminuria, leading to a clinically relevant proportion of false-positive results by ACR [53].

Within the PIERS cohort, dipstick proteinuria performs as well (or poorly) as other methods of assessing proteinuria for prediction of adverse outcomes [54]. Our findings support the view that once significant proteinuria has been identified (by dipstick, PrCr ratio or 24-h collection), further proteinuria assessment *should not* be used to guide clinical decision making related to either short- or long-term prognosis. Rather, the serum creatinine value should be used to monitor renal function and risk in women with pre-eclampsia [55].

Maternal Risk Stratification at Time of Disease

In the Community

A research priority has been to improve the capacity of community-level health-care providers to assess the risk borne by women with pregnancy hypertension. To that end, the miniPIERS model has been developed and validated [9•]. The miniPIERS model is limited to demographics, symptoms and signs [parity (nulliparity vs. parity); gestational age on admission, headache/visual disturbances, chest pain/dyspnea, vaginal bleeding with abdominal pain, systolic blood pressure, and dipstick proteinuria]. The miniPIERS model was well calibrated and has an AUC ROC of 0.77 [95 % CI 0.74-0.80]. A predicted probability ≥25 % to define a positive test classified women with 85.5 % accuracy.

The miniPIERS model has been integrated with evidence-based decision algorithms to produce the PIERS on the Move mobile health (mHealth) smartphone application (app) to guide the diagnosis, risk assessment and initial management of women with pre-eclampsia [56•]. Where relevant, the PIERS on the Move decision algorithms are based on the 2011 WHO recommendations for pre-eclampsia treatment [4]. The PIERS on the Move app has been modified to either include or exclude the addition of phone oximetry through the smart phone audiojack. Pulse oximetry independently identifies women at incremental risk for the adverse maternal outcomes associated with pre-eclampsia [57]. Both versions of the app are being used in the Community Level Interventions for Pre-eclampsia (CLIP) cluster randomized controlled trials recruiting in Nigeria, Mozambique, Pakistan and India that will recruit a total of≈80,000 pregnant women (http://clinicaltrials.gov/ct2/show/NCT01911494).

We believe that a version of the miniPIERS mHealth app, especially with pulse oximetry, will become a useful tool for practitioners in their standalone practices and for rural and remote settings in more developed countries.

In Facility

The fullPIERS model utilizes resources available at hospitals and some primary health centers. It includes demographics, symptoms, signs and laboratory tests [gestational age, chest pain or dyspnea, oxygen saturation, platelet count, and serum creatinine and aspartate transaminase (AST) concentrations] [10]. In the fullPIERS data set, concentrations of AST, alanine transaminase (ALT) and lactate dehydrogenase (LDH) were so highly correlated that only one test should be required to gain the same amount of clinically useful information. In our opinion, AST is preferable as it is less hepatospecific than ALT, but does not rise physiologically in pregnancy, unlike LDH. The fullPIERS model predicts adverse maternal outcomes within 48 h (AUC ROC 0.88 [95 % CI 0.84–0.92]), without significant overfitting, and performs reasonably well (AUC ROC >0.7) up to 7 days after eligibility.

Within the fullPIERS data set, it has been noted that routine coagulation tests are unnecessary in women with pre-eclampsia whose platelet counts are above 150,000 and only definitely indicated once platelet counts fall below 100,000 [58]. As stated above, pulse oximetry is effective at stratifying risk in women with pre-eclampsia (even for predicting non-cardiorespiratory outcomes) [53], and dipstick proteinuria, PrCr ratio and 24-h collections are equally as poor in providing further discrimination of maternal risk once the diagnosis of pre-eclampsia has been made [54]. Heavy proteinuria should not be used as a criterion for delivery for maternal indications in women without pre-existing renal disease [59•].

Translational Biomarkers

It appears that PlGF is the angiogenic biomarker closest to having a direct impact on clinical care [16••, 17•, 18]. Of the 625 women with suspected pre-eclampsia in the industry-funded PELICAN Study, 346 (55 %) developed confirmed pre-eclampsia [16••]; clinicians and the women were masked to the PlGF values during the time of their clinical care. In 287 women enrolled before 35 weeks' gestation, free PlGF concentrations <5th centile for gestational age had high sensitivity (0.96 [95 % CI 0.89-0.99]) and negative predictive value (0.98 [95 % CI 0.93-0.995]) for pre-eclampsia requiring delivery within 14 days. Therefore, PlGF has the ability to confirm the diagnosis of pre-eclampsia and, further, to risk stratify risks in terms of delivery within a fortnight. The AUC ROC for low PlGF (0.87) was greater than all other commonly used tests, singly or in combination (range, 0.58-0.76) [16••]. Similar data exist for the sFlt-1/PlGF assay in terms of its diagnostic performance for pre-eclampsia. However, the sFlt-1/PlGF assay may not match PlGF alone for maternal risk stratification performance [60–64]. Currently, it is uncertain how either PlGF or the sFlt-1/PlGF ratio should be used in day-to-day clinical decision making or how angiogenic data should be

integrated into risk stratification tools such as fullPIERS. This is an area of active research.

Fetal Assessment in Women with Pre-eclampsia

Fetal assessment in the management of women with pre-eclampsia was recently reviewed by Gruslin and Lemyre [65]. What is important to note is that the biophysical profile may falsely reassure practitioners about fetal wellbeing in women with pre-eclampsia [66, 67], as has been observed for pregnancies complicated by diabetes and IUGR [68–70].

There is evidence that angiogenic imbalance, as either PlGF alone or in combination with sFlt-1, stratifies perinatal risks for fetuses of pre-eclampsia pregnancies [16••, 60]. Again, how to integrate such data into current management paradigms remains uncertain.

Timing of Delivery

In response to the new SOGC definition of severe pre-eclampsia, any woman with severe pre-eclampsia should be delivered [7••, 8••]. The manner of that delivery will be determined by the woman's gestational age and other obstetric factors.

At Term

The Hypertension and Pre-eclampsia Intervention Trial At Term (HYPITAT) Trial has determined that women at term ($\geq 36^{+0}$ weeks) with either pre-eclampsia or non-proteinuric gestational hypertension are best managed by a policy of induction of labor [71]. Seven hundred fifty-six patients were allocated to induction of labor within 24 h (n=377) versus expectant monitoring (n=379); 117 (31 %) allocated to induction of labor developed poor maternal outcome compared with 166 (44 %) allocated to expectant monitoring (relative risk [RR] 0·71 [95 % CI 0·59-0·86]). Among women randomized $\geq 37^{+0}$ weeks, there were *fewer* cesarean sections associated with a policy of induction (number need to treat for benefit=7 [95 % CI 4.6-13.6]).

Near Term

The recently reported HYPITAT-II Trial (abstract only) recruited 704 women with pre-existing and gestational hypertension and pre-eclampsia from 34^{+0}–36^{+6} weeks' gestation [72••]. Again the intervention was a policy of induction (within 24 h) compared with expectant management. Due to HYPITAT, all women were induced at 37^{+0}. A policy of induction near term was associated with no measurable benefit for mothers (RR 0.44 [95 % CI 0.11-1.67]), but with greater risks of respiratory distress in newborns at all gestational ages (RR 3.01 [95 % CI 1.30-6.99]). We await the greater detail of the trial findings in the full publication.

Remote from Term

Remote from term, randomized controlled trial (RCT), case–control and cohort data support a policy of expectant (versus interventionist) care [73, 74]. Generally, about half of women will remain undelivered 48 h after presentation (timeframe for antenatal corticosteroid administration and effect) and be eligible for expectant management. In RCTs, the *in utero* time gained from eligibility to delivery is about 14 days, whereas in non-RCT studies, the time gained is generally 7–10 days. Expectant management should only be attempted in institutions experienced in the management of pre-eclampsia. Failure to provide obsessive surveillance during expectant management is a life-threatening gap in care [75]. For women who present before 24 weeks' gestation (or local limits of viability), expectant management is unlikely to offer any perinatal advantages while maternal risks persist and rise [74, 76].

Management of Maternal Blood Pressure

Table 3 summarizes the characteristics of the most commonly used agents for both severe and non-severe pregnancy hypertension.

Severe Hypertension (≥160/110 mmHg)

Severe systolic hypertension is an independent risk factor for stroke in pregnancy [77]. The UK 'Confidential Enquiries into Maternal Deaths' has identified failure to recognize the severity of and to treat the severe (particularly systolic) hypertension of pre-eclampsia as the single most serious failing in the clinical care of those women who died from strokes [78, 79], a finding consistent with the Dutch experience [75]. Effective antihypertensives are available in all settings to manage severe pregnancy hypertension [3–6, 7••, 8••, 80]. Blood pressures ≥160 mmHg systolic and ≥110 mmHg diastolic require a response, with immediate targets being to lower blood pressure to under those thresholds within hours [3–6, 7••, 8••]. Such acute elevations in blood pressure may reflect either the development or progression of pre-eclampsia and should precipitate detailed clinical, laboratory and ultrasound assessment of the pregnancy.

The primary choices of agents for treating severe pregnancy hypertension are nifedipine (oral), labetalol (oral and intravenous) and hydralazine (parenteral). In recent national recommendations (UK, Canada), there has been a move away from recommending parenteral agents as first-line therapy to

Table 3 Antihypertensives for severe and non-severe pregnancy hypertension

Agent/indication	Dosage	Onset	Peak	Duration	Comments
Severe hypertension					
Hydralazine	Start with 5 mg IV; repeat 5–10 mg IV every 30 min, or 0.5–10 mg/h IV, to a maximum of 20 mg IV (or 30 mg IM)	5 min	30 min	2 - 4 h	May increase the risk of maternal hypotension
Labetalol IV	Start with 20 mg IV; repeat 20–80 mg IV every 30 min, or 1–2 mg/min [then switch to oral (max 300 mg)]	5 min	30 min	4 h	Best avoided in women with asthma or heart failure. Neonatology should be informed if the woman is in labor, as parenteral labetalol may cause neonatal bradycardia
Labetalol po	200 mg loading dose; repeat further 200 mg doses every 45 min [then switch to regular oral [max 1,200 mg/day)]	20 min - 2 h	1 - 4 h	8-12 h (dose-dependent)	
Nicardipine IV	Initial infusion rate 2.5-5 mg/h, increasing by 2.5 mg/h every 5 min (max 15 mg/h)	5 min	20 min	4 - 6 h	Currently not recommended as a first line agent by any national or international guideline committee
Nifedipine capsule	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, the intermediate-acting tablets and the slow-release tablets. Avoid nifedipine capsules in women with known coronary artery disease, severe aortic stenosis and preexisting diabetes of ≥15-year duration because of the risks of acute coronary syndromes
Nifedipine intermediate-acting/PA	10 mg tablet; repeat 10 mg doses every 45 min (then switch to regular oral medication) (max 120 mg/day)	30 min	4 h	12 h	
Non-severe hypertension					
Methyldopa	250–500 mg po bid-qid (max 2 g/day)	40 min	3-6 h	12-24 h	There is no evidence to support a loading dose of methyldopa
Labetalol	100–400 mg po bid-tid (max 1,200 mg/day)	20 min - 2 h	1 - 4 h	8-12 h (dose-dependent)	Best avoided in women with asthma or heart failure. Some experts recommend a starting dose of 200 mg po bid
Nifedipine intermediate-acting/PA	10-40 mg tablet po bid-tid (max 120 mg/day)	30 min	4 h	12 h	Staff should be aware of the distinction between short-acting nifedipine capsules, the intermediate-acting tablets and the slow-release tablets
Nifedipine XL preparation	20–60 mg po OD (max 120 mg/day)	60 min	6 h	24 h	

bid twice daily, *IM* intramuscular, *IV* intravenous, *max* maximum, *OD* daily, *po* by mouth, *qid* four times daily, *tid* three times daily

oral agents [3, 7••, 8••], with statements supporting either approach in the recent WHO, ACOG and ISSHP guidelines [4–6]. Nicardipine may provide an option for parenteral management of severe pregnancy hypertension [81–83], as it appears to be more effective than labetalol at controlling severe hypertension without the risks of hypotension seen with hydralazine [81, 84].

Our preference is for oral agents in non-obtunded women as their use can be initiated by nurses/midwives rather than the common requirement for obstetrician presence for an intravenous agent; the presence of an obstetrician can be delayed because of concurrent activities such as cesarean sections. In summary, our preference is for oral nifedipine (either capsule or intermediate-acting tablet) because it has a more reliable effect than both labetalol and hydralazine and the less frequent occurrence of drug-induced hypotension [7••, 8••]. Nifedipine is safe to use with concurrent $MgSO_4$ [7••, 8••].

Within the context of the PRE-EMPT (PRE-eclampsia-Eclampsia Monitoring, Prevention and Treatment) initiative, Gynuity Health Projects are currently conducting a RCT with a head-to-head comparison of three oral antihypertensives for severe pregnancy hypertension, nifedipine, labetalol and methyldopa (http://pre-empt.cfri.ca/treatment/treatment-gynuity-trial). The results of this trial will be pertinent to all caregivers, but particularly those providing care in less developed countries.

However, while we have a stated preference for nifedipine, and pending the results of the Gynuity trial, we support the ACOG statement, "In women requiring antihypertensive medications for severe hypertension, the choice and route of administration of drugs should be based primarily on the physician's familiarity and experience, adverse effects and contraindications to the prescribed drug, local availability, and cost" [5].

As a rule of thumb, our approach is to reserve nifedipine for use in women with severe pregnancy hypertension and to use either labetalol and/or methyldopa for longer term medication to achieve synergism of effect and to avoid the acute cardiovascular risks associated with nifedipine capsules with beta-blockade. In addition, if a woman experiences an acute elevation in her blood pressure on, say, labetalol, it seems logical to us not to use more of that agent for acute blood pressure control.

Non-severe Hypertension (140-159/90-109 mmHg)

Compared with placebo or no therapy, any antihypertensive therapy will decrease transient severe hypertension (RR 0.50 [95 % CI 0.41–0.61]) (a surrogate risk for stroke [77]), without altering the incidence of other outcomes, including pre-eclampsia and preterm delivery [85]. However, due to concerns related to an effect of both fetal growth velocity and other adverse perinatal outcomes, current guidelines do not give firm recommendations related to blood pressure targets in women with non-severe pregnancy hypertension, other than those with comorbid conditions that mandate normotension [3–6, 7••, 8••]. The definitive CHIPS (Control of Hypertension In Pregnancy Study) RCT, addressing this contentious issue of blood pressure targets in non-severe pregnancy hypertension, will publish its results in 2014 (http://www.thelancet.com/protocol-reviews/09PRT-3980). This RCT will inform the care of women without comorbid conditions; all guidelines mandate targeting normotension in women with conditions such as renal disease and prepregnancy diabetes [3–6, 7••, 8••]. However, the commonly used renoprotective agents [angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs)] should not be used in pregnancy because of their fetotoxic effects associated with increased stillbirth risks [3, 4, 6, 7••, 8••] and possible teratogenicity [3]. ACEIs appear to be reasonable choices during lactation [3, 7••, 8••]. Of the commonly available beta-blockers, atenolol appears to be particularly associated with reduced fetal growth velocity and should be avoided because of the ready availability of alternative agents [3, 5, 7••, 8••]. The commonly used agents used to manage non-severe pregnancy hypertension (and their characteristics) are listed in Table 3 and are supported by all current guidelines [3–6, 7••, 8••].

Magnesium Sulfate Regimens

Magnesium for Eclampsia Prevention and Treatment

It is well recognized that $MgSO_4$ is recommended as the first-line treatment of eclampsia and its prevention, especially in women with severe disease [86–89]. Due to concerns related to maternal safety, cost and resource availability, there has been an interest in alternative regimens for $MgSO_4$ administration, particularly in less developed countries [90, 91].

Therefore, a recent review of 10 RCTs and 16 observational studies evaluated $MgSO_4$ regimens for pre-eclampsia and/or eclampsia in World Bank-classified low and middle income countries (LMICs) [91]. Rates of eclampsia were usually <5 % (median 3.0 %, range 0.0 % to 26.5 %) even when $MgSO_4$ was administered to prevent recurrent eclampsia. Loading dose only regimens (4 g IV+10 g IM) versus loading plus maintenance dosing of 5 g/4 h IM showed no difference in eclampsia recurrence (RR 1.64 [95 % CI 0.48-5.65]). A single study showed less eclampsia recurrence associated with community administration of an $MgSO_4$ loading dose before referral to a facility versus limiting treatment to facilities (RR 0.23 [95 % CI 0.11-0.49]). Clarifying exactly who among women with non-severe pre-eclampsia requires $MgSO_4$, how much women should receive, and for how long remains a research priority.

Magnesium for Neuroprotection

In addition to its use for eclampsia prophylaxis and treatment, in women with pre-existing or gestational hypertension, $MgSO_4$ should be considered as a cost-effective therapy to decrease the risk of cerebral palsy (and 'death or cerebral palsy') in the setting of 'imminent preterm birth' (within the next 24 h) up to 33^6 weeks [92–94].

Long-term Maternal Outcomes

Pregnancy can be regarded as a biological stress test that informs women of their future cardiovascular risk [95–98]. Large-scale epidemiological studies have associated gestational hypertension, and pre-eclampsia in particular, with an increased risk of hypertension, renal disease [99], and cardiovascular and cerebrovascular morbidity and mortality [96, 97, 100–102]. Women who are normotensive but who have had a hypertensive disorder of pregnancy may benefit from assessment of traditional cardiovascular risk markers. However, it is unclear that early testing (and intervention) for traditional cardiovascular risk factors will decrease subsequent vascular events. Pre-eclampsia may be associated with a small increased risk of subsequent thromboembolism [100, 103]. In addition, an excess of microalbuminuria has been documented, but may reflect underlying renal disease or act as an independent marker for cardiovascular risk [24, 104, 105].

Conclusions

The care of women with pre-eclampsia is evolving. With the greater clarity in the definition of 'severe' pre-eclampsia afforded by the 2014 SOGC guidelines [7••, 8••], clinicians will have clearer guidance about when delivery is required and when expectant management, supported by cost-effective and evidence-based assessment and surveillance [9•, 10, 47•, 54, 56•, 57], may be offered. It is probable that the biophysical profile does not have a place in such surveillance [66, 67].

Ongoing developments regarding our understanding of the origins and types of pre-eclampsia [17•] are already paying dividends in terms of improving our ability to identify who will get, and who has, the disease [14, 15, 16••, 17•, 18, 20, 21, 22••, 23, 26–30] and how long they are likely to remain pregnant [9•, 10, 16••]. Commercially available biomarkers appear to reflect the presence of an imperfect placenta rather than be specific to pre-eclampsia [19•].

Such approaches should better direct efforts to prevent pre-eclampsia. While high-dose calcium supplementation appears to reduce the risk of pre-eclampsia, it may be associated with inherent risks [35, 36, 37•]; lowering the calcium dose appears to be equally effective in reducing the incidence of pre-eclampsia and should avoid some of the risks identified with higher doses [38••].

In women with non-severe pre-eclampsia, expectant management is the approach of choice at early and late preterm gestations [72••, 73, 74], with labor induction being the preferred option at term [71]. Due to the risks inherent to severe pregnancy hypertension [77–79], blood pressure should be reduced to non-severe levels using available agents [80]; the CHIPS Trial will inform us about blood pressure targets for women with non-severe pregnancy hypertension. There is insufficient evidence to support non-standard $MgSO_4$ regimens for eclampsia prevention and treatment [91].

We believe that the focus of the global agenda to reduce the largely avoidable burden of pre-eclampsia-related adverse outcomes would best be focused first on the community diagnosis and timely initiation of therapy, as has proven so effective in the UK.

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Compliance with Ethics Guidelines

Conflict of Interest Peter von Dadelszen has received an unrestricted grant-in-aid to support PlGF-related research, particularly related to IUGR. He has also received consultancy fees from Alere International and payments from Christiana Healthcare for work in a DSMB related to an RCT of antibiotics for group B streptococcus in pregnancy. Dr. von Dadelszen receives salary support from the Child & Family Research Institute, UBC.

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