5

Risk factors and predictors of pre-eclampsia

UV Ukah, B Payne, AM Côté, Z Hoodbhoy, P von Dadelszen

"I value screening so that I can appropriately contextualise my risk and plan accordingly. Not for anything, but with other children at home, knowing at 12 weeks that I am higher risk for complications would give me much better lead time to look finding a childcare provider and to budget for it even if I wound up not ultimately needing more advanced care."

Pre-eclampsia survivor

SYNOPSIS

This chapter, reviews the risk factors for pre-eclampsia, but focuses more on the predictors of pre-eclampsia and, to a lesser extent, other placental complications of pregnancy, especially gestational hypertension and intrauterine growth restriction (IUGR). Early prediction of pre-eclampsia will aid in identifying women at highest risk, allow for preventative interventions such as low-dose aspirin, and guide surveillance to avoid severe complications. The strongest risk factors for pre-eclampsia include previous pre-eclampsia, antiphospholipid antibody syndrome, pre-existing medical conditions and multiple pregnancy. Currently, there is no single predictor of pre-eclampsia among women at either low or increased risk of pre-eclampsia that is ready for introduction into clinical practice, but the most promising predictors are the angiogenic factors and uterine artery Doppler velocimetry combined with other biochemical factors using multivariate models.

However, it should be stated that very few of the informative data have been derived from populations of women who bear the greatest burden of experiencing complications of pre-eclampsia, namely women in less-developed countries.

WHAT TO PREDICT

In our opinion, this area of research and clinical practice has been confused by a number of factors, of which we emphasise three.

First, and of particular relevance for colleagues in less-resourced settings, is the need to identify women who are at increased risk for any placenta-derived antenatal complication, whether pre-eclampsia, gestational hypertension, or intrauterine growth restriction (IUGR). Clinically, what matters is to identify those women who would most benefit from careful surveillance during their pregnancy, ideally using the model of accelerating antenatal visits (every 4 weeks until 27 weeks, every 2 weeks between 28 and 35 weeks, and weekly from 36 weeks) that has largely become the standard of care throughout more-developed communities, and, potentially, prophylaxis against later disease (e.g., low-dose aspirin and calcium supplementation (see Chapter 6)). It should be remembered that this

pattern of antenatal surveillance was developed in Edinburgh largely to identify women with pre-eclampsia, so that they could be delivered before complications arose. Once effective screening methods have been identified, societies need to determine what false-positive rate they will accept, with what sensitivity, to identify an enriched cohort of pregnant women who will most benefit from increased surveillance. Therefore, what may really matter is the ability to exclude women who will go on to have uncomplicated pregnancies. For these women, the risks of pregnancy then focus around the time of birth and the early puerperium. Such risks are those of the other leading causes of maternal mortality, obstetric haemorrhage, sepsis and prolonged labour. Such women may benefit from the WHO four-visit model of antenatal care, which failed to show benefit when subjected to a randomised controlled trial[1]. By design, the WHO four-visit model misses the increased maternal and perinatal risks that derive from the majority of cases of pre-eclampsia that have their first clinical manifestations between 36 weeks' gestational and delivery.

Second, has been the conflation of all forms of pre-eclampsia (whether of primarily placental (early-onset) or maternal (late-onset) origin) into a single diagnosis; we now recognise that, other than the commonality of the presence of a placenta, the pathways to disease vary widely between placental and maternal disease[2]. The same issue arises for so-called IUGR. Many, even most, pregnancies in which either the fetal abdominal circumference or estimated fetal weight drops below the 10th centile by ultrasound are not complicated (other than by resulting investigations and interventions) – rather, the fetus is constitutionally small[3].

Third, how can we be certain that the pathways to pre-eclampsia are shared by women in more-developed countries (who usually have a prolonged coitarche-to-pregnancy interval, often using non-barrier contraception, and are increasingly often over 30 years-old at first ongoing pregnancy and overweight or obese) and women in less-developed countries (who are often young and anaemic, bear a burden of chronic infection, and conceive within months of first intercourse)? It may be that screening biomarkers that are shown to be effective in more-developed countries in ongoing research will fail women in less-developed settings – this is a research priority mentioned below. Conversely, reverse innovation of screening biomarkers that are effective in less-developed settings may not have clinical utility in more-developed country populations.

In the following sections, the risk factors and predictors of pre-eclampsia are discussed in detail.

RISK FACTORS

Risk factors are any attributes or exposures that increase the chances for an individual to develop a disease[4]. Risk factors for pre-eclampsia include a wide array of conditions that reflect the complexity of the disease process and their strengths of association are quantified using risk ratios or odds ratios[5]. These can be categorised based on familial factors, demographic factors, past medical or obstetric history, pregnancy-associated factors, paternal factors and miscellaneous factors. The following risk factors are summarised in Table 5.1.

Familial factors

Pre-eclampsia is a complex disorder, which is seen to be inherited in a familial pattern[6]. The placenta plays a central role in the pathogenesis of pre-eclampsia, thus implying that both maternally and paternally derived fetal genes may play a role in the development of the disease[6]. Pre-eclampsia complicating any of a given woman's pregnancies is a significant risk factor for pre-eclampsia complicating her daughters' pregnancies[7]. Chesley and Cooper reported that for those women who experienced pre-eclampsia, the rate of disease was higher in sisters (37%), daughters (26%) and grand-daughters (16%) when compared with daughters-in-law (6%)[8]. A recent review suggested that those with a family history of pre-eclampsia are at an increased risk for this disease (RR 2.90, 95% CI 1.70–4.93)[9]. A large population-based study reported a significantly higher risk of pre-eclampsia in sisters diagnosed with pre-eclampsia (RR 2.6, 95% CI 1.8–3.6)[10]. This risk increased further with the severity of disease (i.e., 2+ proteinuria) (RR 3.7, 95% CI 2.5–5.5)[10].

Further, a large Danish study reported that a history of early- or intermediate-onset pre-eclampsia in the mother or sister increased the risk of the similar form of pre-eclampsia by at least 150% compared with an absence of such family histories. For those women with a history of late-onset pre-eclampsia, this risk only increased by 73%[11].

Table 5.1 Summary of risk markers for pre-eclampsia (modified from PRECOG-I and -II[139])

Maternal				
		Current pregnancy		
Demographics and family history	*Past medical or obstetric history*	*First trimester*	*Second or third trimester*	*Paternal*
	Previous pre-eclampsia	**Multiple pregnancy**		
	Antiphospholipid antibody syndrome			
	Pre-existing medical condition(s)			
	• Pre-existing hypertension or booking dBP ≥90 mmHg			
	• Pre-existing renal disease or booking proteinuria			
	• Pre-existing diabetes mellitus			
Afro-Caribbean or South Asian race	Lower maternal birth weight and/or preterm delivery	Short maternal stature ≤164 cm/5'5"	Excessive weight gain in pregnancy	Paternal age ≥45 years
Maternal age ≥35–40 years	Thrombophilias	Overweight/obesity		
Family history of pre-eclampsia (grandmother, mother or sister)	Increased pre-pregnancy triglycerides, total cholesterol and/or non-HDL-cholesterol	Reduced physical activity		Mother had pre-eclampsia
Family history of early-onset cardiovascular disease	Non-smoking	First ongoing pregnancy		Fathered pregnancy complicated by pre-eclampsia with another partner
Rural location (LMICs)	Cocaine and/or methamphetamine use	New partner		
	Previous miscarriage at ≤10 weeks with same partner	Short duration of, or reduced, exposure to sperm of current partner		
	Previous pregnancy complicated by IUGR	Reproductive technologies		
	Maternal uterine anomaly	Inter-pregnancy interval ≥4 years		
	Increased stress	Mental health (depression and/or anxiety)		
		Booking sBP ≥130 mmHg	Elevated BP (gestational hypertension)	

continued

Table 5.1 *continued*

Maternal				
		Current pregnancy		
Demographics and family history	*Past medical or obstetric history*	*First trimester*	*Second or third trimester*	*Paternal*
Rural location (LMICs)	(Recurrent miscarriage)	Booking dBP ≥80 mmHg	Gestational proteinuria	
		Vaginal bleeding in early pregnancy		
		Gestational trophoblast disease		
		Anaemia with low vit C and E intake (LMICs)		
		Severe anaemia (Hb <7.0 g/L)		
		Abnormal serum screening analytes	Abnormal serum screening analytes	
		Investigational laboratory markers	Investigational laboratory markers	
		Reduced 25(OH)-vit D	Abnormal uterine artery Doppler	
		Female fetus (early-onset)	Infection during pregnancy (e.g., UTI, periodontal disease)	
		Male fetus (late-onset)		
		Congenital fetal anomalies		

BP, blood pressure; dBP, diastolic blood pressure; HDL, high-density lipoprotein; LMICs, low- and middle-income countries; sBP, systolic blood pressure; UTI, urinary tract infection; vit, vitamin

In addition, a paternal familial component has been suggested; the partners of men who were the product of a pregnancy complicated by pre-eclampsia were, themselves, more likely to develop pre-eclampsia than women whose partners were born of normotensive pregnancies[12].

Women with a maternal and/or paternal history of hypertension or diabetes mellitus had a statistically significant increased risk to develop pre-eclampsia[13,14].

Demographic factors

Age

Extremes of maternal age have been associated with risk of pre-eclampsia/eclampsia[2]. Maternal age ≥40 years has been associated with an increased risk (OR 1.49, 95% CI 1.22–1.82)[15]. The WHO Multicountry Survey of Maternal and Newborn Health reported that women ≥35 years were at high risk of pre-eclampsia, though not eclampsia. However, women ≤19 years of age were at high risk for eclampsia, but not a diagnosis of pre-eclampsia – probably related to underdiagnosis of pre-eclampsia in populations of women without full antenatal surveillance[16].

Ethnicity

Women belonging to Afro-Caribbean or South Asian ethnicity have been shown to be at higher risk when compared with Caucasians[15,17]. African-American women with severe pre-eclampsia demonstrate higher blood pressures and require more antihypertensive treatment, while Caucasian women have a higher incidence of HELLP (haemolysis, elevated liver enzymes and low platelet) syndrome[18].

Past medical or obstetric history

Maternal birth weight

Women with low birth weight (<2500 g) have been shown to have double the risk of experiencing pre-eclampsia (OR 2.3, 95% CI 1.0–5.3) when compared with women who weighed 2500–2999 g at birth[15]. Further, the risk increased four-fold for those women who weighed <2500 g at birth and were overweight as adults[19]. A Danish cohort study reported that there was an increased frequency of pre-eclampsia in women who were born prematurely and were small-for-gestational age[20].

Stature and pre-pregnancy body mass index

A large population-based study reported that short stature of women (≤164 cm/5'5") predisposed them to an increased risk of severe pre-eclampsia[21]. Women who are overweight or obese are known to be at increased risk for pre-eclampsia[22]. A recent meta-analysis concluded that overweight/obesity as well as maternal adiposity is associated with an increased risk of pre-eclampsia[23]. Increased BMI is an important risk factor for pre-eclampsia and severe pre-eclampsia with an attributable risk of 64%[24]. This risk[25] may be increased two- to three-fold as BMI increases from 21 kg/m^2 to 30 kg/m^2.

Pre-existing medical conditions

Pre-gestational diabetes (type 1 and type 2) is associated with two- to four-fold increased risk of pre-eclampsia[10,26,27]. In addition, pre-gestational diabetes may be a significant contributor to new-onset late-postpartum pre-eclampsia[28].

Lecarpentier *et al.* reported that 23% of women with chronic hypertension were at risk of superimposed pre-eclampsia. Mean arterial pressure (MAP) ≥95 mmHg was a good predictor of this risk[29]. A recent systematic review by Bramham *et al.* reported that the relative risk of superimposed pre-eclampsia in women with chronic hypertension was nearly eight-fold higher than was pre-eclampsia in the general pregnancy population[30]. Adverse neonatal outcomes such as preterm delivery (<37 weeks of gestation), low birth weight and perinatal death in this group of women were three-to-four times as likely[30].

Women with both chronic hypertension and pre-gestational diabetes are eight times more likely to be diagnosed with pre-eclampsia when compared with women without either condition[31].

Pre-eclampsia may occur frequently in pregnant women with chronic kidney disease, lupus nephropathy, as well as diabetic nephropathy[32]. For women with diabetes, proteinuria of either 190–499 mg/day or ≥+2 on urine dipstick at booking[33,34] is associated with a significantly higher risk of pre-eclampsia.

A meta-analysis of 74 studies evaluating hyperlipidaemia and risk of pre-eclampsia reported that elevated levels of total cholesterol, non-high density lipoprotein (HDL)-C and triglycerides are observed during all trimesters of pregnancy, while lower levels of HDL-C are seen during the third trimester[35].

Thrombophilias

Special mention should be made of testing for inherited thrombophilias (such as factor V Leiden mutation, prothrombin gene mutation, protein C or S deficiency, or antithrombin III deficiency) or acquired thrombophilia (such antiphospholipid antibodies). Among the genetic thrombophilias, a recent meta-analysis of 31 case–control studies concluded that factor V Leiden single nucleotide polymorphism (SNP) is associated with an increased risk of pre-eclampsia. No association was found between methylene tetrahydrofolate reductase (MTHFR) SNP and prothrombin SNP and risk of pre-eclampsia[36].

The antiphospholipid syndrome (APS) is a systemic autoimmune disorder with raised titres of antiphospholipid antibodies and is characterised by arterial and venous thrombosis, and adverse pregnancy outcomes[37]. A meta-analysis of 28 studies reported that the risk of pre-eclampsia was two times higher in women who tested positive for lupus anticoagulant and anticardiolipin antibodies (OR 2.34, CI 1.18–4.64 and OR 1.52, CI 1.05–2.20, respectively)[38]. However, this association was only reported in case–control, and not in cohort, studies[38].

While we recognise that this is a very controversial area, in our opinion, thrombophilia screening is not recommended specifically for investigation of previous pre-eclampsia or other placental complications, with the exception of testing for antiphospholipid antibodies if the woman meets the clinical criteria for the diagnosis[39,40].

Parity

Pre-eclampsia is recognised to more commonly complicate a woman's first pregnancy[6]. A large population-based study reported that nulliparous women were at increased risk of pre-eclampsia compared with parous women (OR 3.6, 95% CI 2.6–5.0)[41]. A recent population-based cohort study reported that nulliparity significantly increased the risk of late-onset pre-eclampsia when compared with early-onset disease[42].

Interval between pregnancies

The risk of pre-eclampsia is generally lower in the second pregnancy if conceived with the same partner. After adjustment for the presence or absence of a change of partner and maternal age, the odds for pre-eclampsia for each 1-year increase in the birth interval were increased (OR 1.12, 95% CI 1.11–1.13)[43]. In a large cohort study, a birth interval of more than 4 years increased the risk of pre-eclampsia in women who had no prior history (OR 1.4, 95% CI 1.2–1.6)[44].

Previous miscarriages

Analysis of data obtained from the Norwegian Mother and Child Cohort Study suggested that there may be an increased risk of pre-eclampsia for women with recurrent miscarriages (adjusted OR 1.51, 95% CI 0.80–2.83), although this was not statistically significant[45]. Similar findings were reported from a Canadian study where history of prior abortion had no effect on risk of pre-eclampsia[46]. However, for women who had recurrent spontaneous abortions and infertility treatment, a three-fold increased risk of pre-eclampsia was seen compared with controls[45].

Previous pre-eclampsia

Women with a history of pre-eclampsia in a previous pregnancy had an increased risk of pre-eclampsia in the current pregnancy compared with parous women with no previous pre-eclampsia (OR 21.5, 95% CI 9.8–47.2). This association was particularly strong for early-onset, moderate and severe disease[41]. In women with prior pre-eclampsia, greater risk is associated with earlier gestational age at delivery. The risk of recurrent pre-eclampsia was 12% for those who previously delivered at term and increased to 40% for those who delivered before 28 weeks of gestation[44]. Although multiple gestation, change of partner, long inter-pregnancy interval, and high BMI are considered risk markers for the *occurrence* of pre-eclampsia, neither multiple gestation or a different partner in the previous pregnancy with pre-eclampsia[47–49], nor long inter-pregnancy interval[50,51] have been demonstrated to further increase the risk of *recurrent* pre-eclampsia. In contrast, higher BMI in a previous pre-eclampsia pregnancy does further increase the risk of recurrence in a subsequent pregnancy[44]; this is important to emphasise as BMI is a modifiable antenatal risk factor.

Previous pregnancy with gestational hypertension

Pre-eclampsia in a previous pregnancy may 'recur' in a subsequent pregnancy as gestational hypertension, just as gestational hypertension in a previous pregnancy may recur as pre-eclampsia in a subsequent pregnancy. Women with a history of pre-eclampsia have similar rates of either pre-eclampsia (median 15%) or gestational hypertension (median 22%) in a subsequent pregnancy. In contrast, most women with a history of gestational hypertension who experience a subsequent hypertensive pregnancy will experience gestational hypertension again (median of 21%, range 8–47%); far fewer will experience their recurrence as pre-eclampsia (median of 4%, range 1–6%) (4 studies, 1311 women)[52–55]. The gestational age at which gestational hypertension developed in the previous pregnancy does not seem to affect whether the hypertensive disorder of pregnancy in the next pregnancy is gestational hypertension or pre-eclampsia.

Pregnancy-associated factors

Multiple pregnancy

Multiple gestations are a risk factor for pre-eclampsia[56,57]. A multicentre study by Sibai *et al.* reported that women with twin pregnancy had higher rates of gestational hypertension (RR 2.04, 95% CI 1.60–2.59) and pre-eclampsia (RR 2.62, 95% CI 2.03–3.38)[58]. Increased placental mass during a twin gestation may lead to increased circulating levels of soluble fms-like tyrosine kinase-1 (sFlt1), which is a circulating antiangiogenic marker of placental origin, and may play an

important role in pathophysiology of, especially early-onset, pre-eclampsia[59].

Fetal gender

A Norwegian cohort study reported that pre-eclampsia occurred more often in the male fetus for those who delivered at 40 weeks or later. For preterm births (gestational weeks 25–36), the proportion of female offspring in pregnancies complicated by pre-eclampsia was considerably higher than that of males[60]. Despite the preponderance of male fetuses in women with pre-eclampsia, no fetal sex-related differences were found in perinatal outcomes (stillbirth, perinatal or neonatal mortality) in such women[61].

Use of assisted reproductive technology

A recent systematic review reported that assisted reproductive technology (ART) (especially *in vitro* fertilization) was associated with higher risk of gestational hypertension and pre-eclampsia when compared with non-ART pregnancies[62]. Results from the CoNARTaS cohort study reported that hypertensive disorders occurred in 5.9% of singleton and 12.6% of twin ART pregnancies compared with 4.7% of singleton and 10.4% of twin pregnancies in spontaneously conceived pregnancies[63].

Infections

A nested case–control study from the UK reported that antibiotic prescriptions (included as a proxy for acute infection) (OR 1.28, 95% CI 1.14–1.44) and urinary tract infection (UTI) (OR 1.22, 95% CI 1.03–1.45) in pregnancy were associated with an increased risk of pre-eclampsia after controlling for confounders such as maternal age, pre-existing renal disease, diabetes and multiple gestation[64]. A meta-analysis of 40 studies reported that women with a UTI and those with periodontal disease were more likely to develop pre-eclampsia than women without these infections. There was no association between the other maternal infections such as chlamydia, malaria, treated or untreated HIV and group B streptococcal colonisation and risk of pre-eclampsia[65,66].

Congenital malformations

A large retrospective study from the Perinatal Information System database in Uruguay reported that fetal malformation was associated with an increased risk of pre-eclampsia (RR 1.26, 95% CI 1.16–1.37)[67]. Congenital anomalies have also been reported to be more strongly associated with early-onset pre-eclampsia rather than late-onset disease (adjusted OR 2.59, 95% CI 1.66–4.02)[42].

Paternal factors

Paternal age

Epidemiological studies suggest that the risk for pre-eclampsia doubles if the woman has a partner aged >45 years[68,69], perhaps as a result of spermatozoa being damaged owing to genetic mutations that occur with ageing or to environmental factors such as exposure to radiation and heat[22].

Primipaternity and sperm exposure

A landmark study by Robillard *et al.* in 1994 showed that conception within the first 4 months of sexual cohabitation of the couple presented a major risk (40–50% incidence) for hypertension to complicate a pregnancy[70]. However, this risk declined significantly for women after at least 1 year of sexual cohabitation before conception[70]. More recent work by Olayemi *et al.* reported that there was a 4% decrease in the risk of developing hypertension for every month increase in cohabitation[71]. This risk was not statistically significant for pre-eclampsia[71]. Repeated intercourse with the same partner leads to maternal mucosal tolerance to paternal antigens, which may be mediated by seminal vesicle-derived transforming growth factor β (TGFβ)[68].

Paternal medical history

The data for paternal history of cardiovascular disease and risk of pre-eclampsia have been conflicting. In a case–control study, Rigo *et al.* reported that early-onset chronic hypertension and early-onset myocardial infarction in the father was associated with a three-fold increased risk of pre-eclampsia after controlling for other confounders[72]. However, the population-based HUNT study reported that there was no association between the hypertensive disorders of pregnancy and paternal cardiovascular risk factors such as BMI, blood pressure and lipid profile[73].

Miscellaneous factors

Smoking

Cigarette smoking is known to have adverse effects on all organ systems. However, a systematic review of 48 epidemiological studies reported that smoking during pregnancy approximately halves the risk of pre-eclampsia[74]. This protective effect was consistently seen irrespective of parity and severity of disease[74]. The pathophysiology of this relationship is not well established. However, it is proposed that smoking might have effects on angiogenic factors, endothelial function and the immune system, which may contribute to the lowered risk of pre-eclampsia[74]. In an attempt to establish causality between smoking and pre-eclampsia, data from the National Swedish Birth Register showed that smoking in two pregnancies again halves the risk of pre-eclampsia, compared with the risk borne by women who did not smoke in either pregnancy[75].

No significant associations have been observed between smokeless tobacco use and pregnancy-associated hypertension in various studies[76,77]. Therefore, it is proposed that combustion products from cigarette smoke other than nicotine may be responsible for the decreased pre-eclampsia risk seen amongst smokers[76].

Physical activity

Exercise and physical activity is recommended during pregnancy to improve maternal health. In their systematic review, Kasavara *et al.* reported that physical activity had a protective effect on the development of pre-eclampsia (OR 0.77, 95% CI 0.64–0.91), while this effect was not seen in cohort studies (OR 0.99, 95% CI 0.93–1.05)[78]. However, a recent meta-analysis conducted by Aune *et al.* reported that those women who engaged in high levels of physical activity pre-pregnancy and continued to do so during early pregnancy, were less likely (by 35% and 21%, respectively) to develop pre-eclampsia, compared with those who participated in low levels of physical activity[79].

Micronutrient deficiencies

Vitamin D deficiency is commonly reported in women and has been investigated to assess its link with pre-eclampsia. There have been conflicting results regarding the serum concentrations of 25-hydroxy vitamin D and the subsequent risk of developing pre-eclampsia[80,81], mainly owing to small sample size of these studies. A recent large case–control study has reported that maternal vitamin D deficiency, defined as 25-hydroxy vitamin D <30 nmol/L, was associated with double the risk of pre-eclampsia when compared with concentrations >50 nmol/L[82].

The Vitamins in Preeclampsia (VIP) Trial reported that vitamin C (1000 mg) and vitamin E (400 IU) supplements given prophylactically from the second trimester of pregnancy have no effect on reduction in the rate of pre-eclampsia in women at risk[83]. Similar findings have been reported by the WHO multicountry vitamin supplementation survey from India, South Africa and Vietnam[84].

Mental health

Depression and anxiety in the first trimester of pregnancy are known to increase the risk of pre-eclampsia by two- to three-fold[85]. In addition, lifetime stress and perceived stress during pregnancy may double the risk of developing pre-eclampsia; an interaction that may be mediated by the neuropsychoimmunological pathway[86].

Socioeconomic status

In developing countries, rural dwellers were twice as likely to develop pre-eclampsia compared with those living in urban areas. Furthermore, women with concurrent anaemia and poor intake of fruits and vegetables were at higher risk of pre-eclampsia[87]. Severe anaemia (haemoglobin <70 g/L) was associated with a three-fold greater risk of pre-eclampsia in women living in less-developed countries[88]. A lack of antenatal care and less than secondary-level education were pertinent risk factors for risk of pre-eclampsia in these regions[88].

PREDICTION (APPENDICES 5.1–5.3)

At present, maternal characteristics which include well-established risk factors discussed above such as maternal age, nulliparity, pre-existing medical conditions and history of pre-eclampsia, are mostly used to screen for pre-eclampsia by clinicians during antenatal visits[56,57,89]. However, these risk factors are not sufficient as only approximately 30% of women who subsequently develop pre-eclampsia are identified by their use[90]. Pre-eclampsia research is now tailored towards development of a predictive model utilising the risk factors mentioned above

along with measurable clinical and laboratory biomarkers to predict the onset of pre-eclampsia.

In the context of this chapter, we are talking about the prediction of a diagnosis of pre-eclampsia (or other placental complications) occurring at some point in the future, not the prediction of complications (prognosis), or risk stratification, in either individual or populations of women whose pregnancies have been complicated by the clinical syndrome of pre-eclampsia (the focus of much of the Chapter 3). According to WHO, a prediction test should be simple, non-invasive, inexpensive, rapid, easy to carry out early in gestation, impose minimal discomfort or risk on the woman, be a widely available technology, and the test results must be valid, reliable and reproducible[91,92].

The performance of predictive tests is generally summarised in the text and tables as being poorly associated, moderately associated and strongly associated when the positive likelihood ratio (LR+) is <5, 5–9.9 and ≥10, respectively (Appendix 5.1). Similarly, for tests that poorly, moderately or strongly exclude risk, their performance is summarised as negative likelihood ratios (LR-) of >0.2, 0.11–0.2 and ≤0.1, respectively. Other summary statistics used in this chapter are the sensitivity ("true positive rate", the proportion of positives that are correctly identified as such, e.g., the percentage of women who will develop the complication who are correctly identified) and specificity ("true negative rate", the proportion of negatives who are correctly identified as such, e.g., the percentage of women who are correctly identified as not developing the condition) of the test to predict the outcome, namely pre-eclampsia, as well as the area under the receiver-operator characteristic curve (AUC ROC)[93–95].

It should be remembered that nearly all the studies referred to in this section relate to women in more-developed countries. Their relevance to women in less-developed countries is uncertain. It is women in less-developed countries who carry the greatest burden of risk for the complications of pre-eclampsia.

PREDICTORS (UNIVARIABLE ANALYSES)

Clinical examination

Blood pressure

Blood pressure, which forms the basis of diagnosis for pre-eclampsia in all international guidelines, is routinely measured during pregnancy[89]. The Society of Obstetrics and Gynaecologists of Canada (SOGC) recommends measurement of blood pressure using a mercury sphygmomanometer, a validated automated blood pressure device or a calibrated aneroid device[56,57]. As high blood pressure is an indication of the increased vascular resistance observed in pre-eclampsia, there have been studies examining the value of blood pressure measurements using systolic blood pressure, diastolic blood pressure, or MAP indices for the prediction of pre-eclampsia[96–99].

A systematic review and meta-analysis by Cnossen *et al.* evaluated the predictive accuracy of using blood pressure measurements in the second trimester for pre-eclampsia. This review included 34 studies reporting the use of blood pressure measurements (systolic blood pressure, diastolic blood pressure and MAP) in predicting pre-eclampsia for women at low risk[96]. The pooled LRs were weakly associated with developing pre-eclampsia. The authors concluded that no index of blood pressure measurement predicted pre-eclampsia well enough to be clinically useful.

Urine

Proteinuria

Proteinuria is routinely measured during pregnancy, especially in women with new-onset hypertension occurring after 20 weeks' gestation to establish the diagnosis of pre-eclampsia[56,57] (see Chapter 2). Underlying renal disease is a recognised clinical risk factor for pre-eclampsia and as such, documentation of proteinuria early in pregnancy is associated with an increased risk of pre-eclampsia (see Pre-existing medical conditions, above). Recently, significant attention has been devoted to the role of albuminuria, and more specifically for lower levels of albuminuria (or 'microalbuminuria') for the prediction of pre-eclampsia. In a review of the published studies retrieved from a structured literature search (1980 to mid-March 2008), a total of seven studies were performed in early pregnancy (defined as <20 weeks) and 13 studies in late pregnancy (≥20 weeks)[100]. Overall, the negative predictive value of 'microalbuminuria' was high but the test performance was not good enough for clinical use, which is consistent with most other individual prediction tests described in this section. The largest study (N = 2486 women) performed at

11^{+0}–13^{+6} weeks demonstrated an increased albumin : creatinine ratio in women who later developed pre-eclampsia compared with those who did not; however, the combined prediction models incorporating the albumin : creatinine ratio results did not yield to significantly improved AUCs over maternal variables alone[101]. Prediction of pre-eclampsia in early pregnancy (17–20 weeks) by estimating the albumin : creatinine ratio was also performed using high-performance liquid chromatography (HPLC)[102]. In this cohort of 265 women with singleton pregnancy, six developed pre-eclampsia; the AUC to predict pre-eclampsia was 0.753. Although the interpretation is of a good predictive test, this study has not been replicated and, in addition, the impact is limited by accessibility to HPLC in clinical practice, especially in less-resourced settings.

Podocyturia (podocyte : creatinine ratio)

Glomerular epithelial cells (podocytes) are involved in the maintenance of the function and structure of the filtration barrier in the kidney[103]. As a consequence of endothelial dysfunction and disruption of the selective filtration barrier in the kidney associated with pre-eclampsia, these podocytes proteins which include podocin, nephrin, synaptopodin and podocalyxin, lose their functional ability and are shed in urine (i.e., podocyturia)[104,105]. Podocyturia is expressed as podocytes : creatinine ratio and has been shown to be associated with manifestation of renal dysfunction in women with pre-eclampsia[103].

A case–control study by Kelder *et al.* analysed maternal urine mRNA levels of three markers of podocytes (VEGF, nephrin and podocin) using quantitative polymerase chain reaction (qPCR-based analysis)[103]. The urine measurements were collected in the early third trimester. None of the three podocyte markers were strong predictors of pre-eclampsia independently, but a combination of all the markers showed a moderate performance in predicting the occurrence of pre-eclampsia.

Craici *et al.* examined the predictive accuracy of podocyturia in the second trimester using only podocin as a marker in a prospective cohort study[105]. In contrast to the study by Kelder *et al.*, this study reported 100% sensitivity (95% CI 78–100) and 100% specificity (95% CI 92–100) in predicting pre-eclampsia, using podocin staining of blood and urine samples. In addition, this study reported a strong LR+ for predicting the occurrence of any hypertensive disorder of pregnancy.

Another prospective study carried out by Jim *et al.* examined the predictive accuracy of podocyturia (using podocin), nephrinuria and albuminuria in the second and third trimesters from urine samples using cytospin technique[104]. Only albuminuria in this study showed a moderate LR+ for the prediction of pre-eclampsia.

The differences in the predictive accuracy for podocin and nephrin in the three studies above may be owing to different analytic techniques, prevalence of pre-eclampsia, and population (e.g. high-risk women versus unspecified). The study designs and gestational age also differed in the studies. Except in the study by Craici *et al.*, none of the urine markers attained the required predictive LR values for clinical use. Further research is needed to make conclusive statements on the use of podocyturia as a screening test for pre-eclampsia.

Calcium (calcium : creatinine ratio)

As a result of renal dysfunction (decreasing glomerular filtration rate) which occurs in pre-eclampsia, there is an increase in serum creatinine and decrease in calcium, thus a decrease in calcium : creatinine ratio has been reported in some studies[106]. Vahdat *et al.* studied the predictive accuracy of urine calcium : creatinine ratio of 150 women during late second trimester. Using a cut-off value of 0.071 in this study, calcium : creatinine ratio was a poor predictor for pre-eclampsia.

Inositol phosphoglycan-P (IPG : creatinine ratio)

Inositol phosphoglycan-P type (IPG-P) which belongs to the insulin mediator family has been reported to be high in urine in pre-eclampsia[107]. A prospective longitudinal study investigated the use of IPG-P : creatinine ratio as a predictive screening test for pre-eclampsia 2 weeks prior to its onset in 416 women. IPG-P : creatinine ratio had moderate LR- and LR+ and may become a useful screening test for pre-eclampsia up to 2 weeks before diagnosis.

Ultrasound markers

Uterine artery Doppler ultrasonography

Doppler ultrasound is a non-invasive technique, and, in this setting, is used to study the uteroplacental

circulation and changes in blood flow resistance[108]. The flow change can be measured as pulsatility index (PI) or resistance index (RI)[108,109].

As an uncomplicated pregnancy progresses, blood flow resistance in the uterine arteries decreases with gestation owing to invasion of the spiral arteries by the trophoblasts[109–111]. The corollary is that increased impedance to blood flow in the uterine arteries has been observed in pregnancies complicated by impaired trophoblast invasion of the spiral arteries, as occurs with placental pre-eclampsia and IUGR of placental origin[111].

The change in uterine artery blood flow between the first and second trimesters has been examined by screening studies to identify pregnancies at risk of pre-eclampsia and fetal growth restriction[109]. The increase in impedance in the uterine arteries is more reflective of preterm pregnancy complications than those at term, as poor placentation is more associated with early-onset pre-eclampsia[110,111].

Abnormal uterine artery Doppler velocimetry may be defined as bilateral notching with or no notching with mean resistance index (RI) >0.70 (>95th centile), mean RI >0.55 (i.e., >50th centile), or unilateral notching with mean RI >0.65 (>90th centile), at 22–24 weeks[56,57].

A few studies have examined abnormal uterine artery resistance during the first and second trimesters for prediction of pre-eclampsia[108,112]. Using a case–control design, Bolin *et al.* measured uterine artery PI in the first and second trimesters as part of routine antenatal screening[109]. Uterine artery PI was expressed in multiples of median (MoM) values and the predictive accuracy for preterm pre-eclampsia was assessed. The uterine artery PI had a poor predictive ability for identifying women at risk of preterm pre-eclampsia.

However, a retrospective observational study by Napolitano *et al.* evaluated uterine artery Doppler PI as a predictor of early-onset and preterm pre-eclampsia in the first and second trimesters[112]. The uterine artery PI was adjusted for gestational age and the PI MoM ratio between the second and first trimesters (uterine artery ratio) was compared with the PI MoM mean difference between the second and the first trimesters (uterine artery difference). For the prediction of early-onset pre-eclampsia, the AUC ROC values were 0.786 (95% CI 0.703–0.869) for the uterine artery ratio and 0.851 (95% CI 0.753–0.950) for the mean uterine artery difference. For the prediction of preterm pre-eclampsia, the AUC ROC of the uterine artery ratio and mean uterine artery difference were 0.701 (95% CI 0.626–0.776) and 0.705 (95% CI 0.599–0.812), respectively. The study concluded that the mean uterine artery difference was the best index for predicting pre-eclampsia and a better predictor of early-onset pre-eclampsia.

Two reviews examining Doppler studies as an individual predictor of pre-eclampsia were found. The review by Papageorghiou *et al.* investigated the use of uterine artery Doppler measurement in the second trimester for the prediction of pre-eclampsia using findings from 15 studies[108]. The sensitivities reported in these studies ranged from 26 to 89% and the specificities ranged from 86 to 96%. The pooled LR+ and LR- were 5.9 and 0.55, respectively, suggesting that second trimester Doppler measurement had a moderate predictive value for pre-eclampsia. However, the studies included in this review differed in Doppler techniques, definition of abnormal flow velocity and pre-eclampsia, populations and disease incidence.

The latter review by Cnossen *et al.* evaluated the accuracy of uterine artery Doppler for predicting pre-eclampsia in low- and high-risk women[96]. Seventy-four studies that reported uterine artery Doppler data in the first and/or second trimesters were included in the review. The review concluded that uterine artery Doppler velocimetry was more accurate in second trimester for prediction than in the first trimester and PI with notching had the best predictive accuracy for pre-eclampsia in both high- and low-risk women. Again, the review was limited by the different Doppler indices used by the included studies.

In conclusion, uterine artery Doppler PI may be a moderate predictor of pre-eclampsia and may be used to 'rule in' pre-eclampsia risk in the second trimester. However, owing to inconsistencies reported in the studies, further studies are required.

Laboratory markers

The markers of pre-eclampsia risk that become available in the second and third trimesters are based on the pathophysiological changes that characterise pre-eclampsia and precede clinical disease. Many have been evaluated, and they

include measures of the following: placental perfusion and vascular resistance (e.g., mean second trimester blood pressure, 24-hour ambulatory blood pressure monitoring, Doppler ultrasound); cardiac output and systemic vascular resistance; fetoplacental unit endocrinology (e.g., pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) in the first trimester, and alpha fetoprotein, hCG and inhibin A in the early second trimester); renal function (e.g., serum uric acid or microalbuminuria); endothelial function and endothelial–platelet interaction (e.g., platelet count, antiphospholipid antibodies, or homocysteine); oxidative stress (e.g., serum lipids); and circulating pro- and anti-angiogenic factors[113,114].

There have been many systematic reviews of primary studies evaluating clinically available biomarkers as well as Doppler ultrasound interrogation of the uterine and umbilical arteries[115–117]. Tests have been chosen for study based on their association with adverse pregnancy outcomes, including pre-eclampsia. Notable examples are serum analytes involved in maternal serum screening for trisomy 21 (4 studies, 427,751 women)[118], serum uric acid measured before 25 weeks (5 studies, 572 women)[119], and Doppler ultrasonographic interrogation of the uterine artery (74 studies, ~80,000 women)[96]. The methodological quality of the primary studies is very variable, related to women enrolled, gestational age at testing, test performance (such as different Doppler sampling techniques or definitions of abnormal flow velocity waveform), and criteria for the diagnosis of pre-eclampsia.

As markers of the fetoplacental unit are commonly used for trisomy 21 screening, it has been proposed that these markers be used for pre-eclampsia risk estimation, in combination with clinical markers. It will be necessary to evaluate whether maternal serum screening for the sole purpose of pre-eclampsia screening, in combination with clinical markers and possibly uterine artery Doppler, leads to improved outcomes. For the moment, further studies are needed before widespread clinical use of serum screening for pre-eclampsia can be advocated, either in high- or low-risk populations. In addition, it must be acknowledged that with the development of non-invasive prenatal testing[120], the use of maternal serum screening might soon become obsolete.

Endothelial dysfunction tests/placental proteins

High-sensitivity C-reactive protein (hs-CRP)

hs-CRP is a systemic inflammatory marker which is produced by the placenta and released into the maternal circulation[121]. This marker can be found in fetal urine and amniotic fluid, and is sensitive to inflammation and tissue damage. Studies have reported an observed increase in maternal hs-CRP level in pre-eclampsia and other adverse pregnancy outcomes. Kashanian *et al.* conducted a prospective cohort study of 394 women evaluating the predictive accuracy of serum hs-CRP for pre-eclampsia in the first trimester[121]. The result from this study show poor LRs of hs-CRP for the prediction of pre-eclampsia.

Fibronectin

Fibronectin, which is released by the placenta, is associated with endothelial damage and inflammation in pre-eclampsia. Higher plasma levels of fibronectin have been reported in women with pre-eclampsia compared to uncomplicated pregnancies leading to research on its predictive ability for pre-eclampsia. A systematic review by Leeflang *et al.* evaluated the predictive ability of fibronectin in five studies[122]. These studies measured total and/or cellular fibronectin in the first or second trimesters. Fibronectin had a pooled moderate LR+ and, therefore, may be a useful test for predicting pre-eclampsia.

Angiogenic factors

Placental growth factor

PlGF, which is a member of the vascular endothelial growth factor (VEGF) family, is a pro-angiogenic factor produced by the syncytiotrophoblast[123,124]. PlGF is at lower maternal circulating concentrations at time of disease with pre-eclampsia, compared with normal pregnancy[123–125]. PIGF assessment point-of-care platforms currently are available[3,126,127].

Ghosh *et al.* evaluated maternal serum PlGF as a predictive test in the second trimester for predicting early-onset pre-eclampsia in a prospective cohort of 722 women[123]. In this study, PlGF was poorly associated with pre-eclampsia as a predictive test. Another study by Ghosh *et al.* compared serum PlGF measurements in the first trimester with measurements in the second trimester for predicting

early-onset pre-eclampsia[128]. Although PlGF performed better in the second trimester compared with the first trimester measurements, both performances were poor for the prediction of pre-eclampsia, as confirmed in an independent cohort of high-risk women in their second trimester to predict early-onset pre-eclampsia[128,129].

In all the aforementioned studies by Ghosh *et al.*, PlGF concentrations were measured by enzyme linked immunosorbent assay (ELISA) technique using the DRG PlGF Enzyme Immunoassay Kit and early-onset pre-eclampsia was defined as pre-eclampsia diagnosed by 32 weeks' gestation[123,128,129].

Chappell *et al.* assessed PlGF in 625 women in their second and third trimester for the prediction of pre-eclampsia with delivery within 14 days[125]. In this prospective cohort multicentre study, plasma PlGF concentration was measured using the Alere Triage® assay. Using a cut-off of PlGF below the 5th centile, PlGF was strongly associated with a negative likelihood of pre-eclampsia with delivery within 14 days of diagnosis.

There are notable differences in the predictive performance and quantification methods of PlGF and in the incidence of pre-eclampsia among these studies investigating PlGF as an independent predictor of pre-eclampsia.

Soluble fms-like tyrosine kinase 1 (sFlt-1 : PlGF ratio)

sFlt-1 is an anti-angiogenic factor produced by the placenta. It antagonises the activities of VEGF and PlGF by binding to them[90,124]. This results in reduction of the free circulating levels of VEGF and PlGF, as observed in women with pre-eclampsia. Some studies have reported that the sFlt-1 : PlGF ratio can be used to identify patients at risk of pre-eclampsia[90,130].

One of these studies was conducted by Engels *et al.* and measured serum samples of sFlt1 : PlGF ratio using automated Elecsys system and assessed its utility in the second and third trimester for predicting pre-eclampsia and HELLP syndrome[130]. Compared with PlGF alone or sFlt1 alone, sFlt1 : PlGF ratio gave the best predictive accuracy for pre-eclampsia and was strongly associated with a positive likelihood of developing pre-eclampsia.

Teixeira *et al.* investigated the predictive value of PLGF, sFlt-1 and sFlt-1 : PLGF ratio in a prospective longitudinal study[131]. Maternal plasma concentrations were measured in 71 high-risk women using a commercial kits (R&D Systems) in their second trimester. In this study, the sFlt-1 : PLGF ratio had a better discriminative ability (AUC ROC 0.95) for the prediction of pre-eclampsia compared with only PlGF (AUC ROC of 0.90) or sFlt-1 (AUC ROC 0.78).

Another prospective study evaluated serum sFlt-1 : PlGF ratio as a predictor of pre-eclampsia in high-risk women[132]. Blood samples were measured in the second and third trimester using electrochemiluminescence technology (Roche). The third trimester sFlt-1 : PlGF ratio performed better than second trimester and was a moderately associated with a negative likelihood for pre-eclampsia.

A nested case–control study by Forest *et al.* evaluated the serum sFlt-1 : PlGF ratio in the second and early third trimesters[133]. sFlt-1 was measured by ELISA using the Quantikine Human Immunoassay (R&D Systems) and PlGF was measured using an automated immunoassay analyzer (DELFIA System, PerkinElmer). The sFlt-1 : PlGF ratio was moderately well associated with later early-onset pre-eclampsia. This contrasts with a similar nested case–control study evaluating serum sFlt-1 : PlGF ratio measured in the late second trimester using the R&D Systems assay and which reported strong associations for predicting early-onset pre-eclampsia in high risk women[134].

Except for a study by McElrath *et al.*[124], all other included studies in this chapter support growing evidence that sFlt1 : PlGF ratio has good potential as a predictive test for pre-eclampsia in the third trimester, especially in high risk women. The study by McElrath *et al.* quantified plasma sFlt-1 and PlGF concentrations measured in the second trimester using the Abbott Diagnostics' platform and showed poor association for the prediction of pre-eclampsia[124]. The contradicting results from this study may have been owing to the use of a different measurement platform and the use of PlGF : sFlt-1, in contrast to the sFlt1 : PlGF ratio used in other studies.

PREDICTING PRE-ECLAMPSIA (MULTIVARIABLE ANALYSES)

No single clinical, blood or ultrasonographic test reaches the ideal of ≥90% sensitivity and specificity for the prediction of pre-eclampsia. Only Doppler ultrasound (i.e., any or unilateral notching and/or

elevated RI) has a sensitivity >60%, particularly when testing is performed in women at increased risk (vs. low risk) of developing pre-eclampsia, in the second (vs. the first) trimester, and for predicting severe and early-onset pre-eclampsia (rather than milder forms of the disease).

Therefore, as there is no single test that predicts pre-eclampsia with sufficient accuracy to be useful clinically[91], interest has grown in the development of multivariable models that include both clinical and laboratory predictors, available at booking and thereafter in pregnancy[135].

The largest relevant studies have been performed by investigators at King's College, London, UK[101]. For example, at 11–14 weeks, a combination of MAP, uterine artery PI, PAPP-A and PlGF was able to identify 93% of early-onset pre-eclampsia, 36% of late-onset pre-eclampsia, and 18% of gestational hypertension such that 20% of women identified as being screen positive developed a hypertensive disorder of pregnancy; this is consistent with other studies[136].

In specialised clinics, women at increased risk of pre-eclampsia may benefit from this type of risk stratification followed by specific preventative intervention(s); however, this is yet to be proven. Similarly, screening of nulliparous or otherwise low risk women is not yet recommended. Prospective longitudinal studies are needed to assess the validity of published observations in other patient populations where some models have performed differently[137]. Future studies should also distinguish the ability of screening approaches to predict pre-eclampsia that is more severe or that which occurs early (vs. at term). Clinicians are encouraged to support clinics investigating predictive models.

In the SCOPE (Screening for Pregnancy Endpoints) Consortium cohort[138], nine clinical predictors of (almost exclusively, late-onset) pre-eclampsia (many of which were identified by PRECOG[139] and NICE 2008[140]) were identified among nulliparous women carrying singleton pregnancies: one protective (miscarriage at ≤10 weeks' gestation with the same partner) and eight associated with increased risk (younger maternal age, higher mean arterial blood pressure, higher BMI, family history of pre-eclampsia, family history of coronary heart disease, woman with lower birth weight, vaginal bleeding during early pregnancy and short duration of sexual relationship). Of note, the performance of this model was not enhanced by knowledge of uterine artery Doppler results. Using the model, which remains to be validated, the probability of pre-eclampsia would increase from 5 to 10% and half of women who go on to develop pre-eclampsia would be detected.

Clinical history/maternal characteristics

The most common clinical risk factors associated with pre-eclampsia include first pregnancy/primigravidity, maternal age, diabetes, history of pre-eclampsia and other hypertensive disorders of pregnancy, family history of pre-eclampsia, and long inter-pregnancy interval[56,57,89,90]. Women with a history of pre-eclampsia are at increased risk (16–65%) of developing pre-eclampsia in a subsequent pregnancy depending on the onset or severity of the disease in the previous pregnancy[140]. The risk of recurrence for women who had pre-eclampsia is approximately 25% for women who also had HELLP syndrome, about 55% for those who had preterm delivery (<28 weeks)[140] and approximately 65% for women who had early-onset pre-eclampsia[141]. In addition, the increased risk for developing pre-eclampsia for women with a history of gestational hypertension ranges from 2 to 9%[140,141] and the reported RR of pre-eclampsia for a woman with a history of chronic or gestational hypertension is RR 8.9, CI 5.7–13.8 and RR 9.8, CI 4.9–19.1, respectively[141].

However, only a few studies have reported the predictive abilities of the clinical factors for pre-eclampsia, most often in combination with other potential predictive markers as clinical risk factors are not very useful predictors individually[90].

Maternal characteristics with biomarkers (placental protein 13, PAPP-A and free beta subunit of hCG)

Placental protein (PP)-13, PAPP-A and free beta subunit of hCG (β-hCG) are produced and secreted by the syncytiotrophoblast and are involved in implantation, trophoblast invasion and remodelling of the spiral arteries[97,142,143]. In healthy pregnancies, there is an increase in PP-13 and free β-hCG from the first trimester which decreases with gestation, whereas in pre-eclampsia, PP-13 and free β-hCG are reportedly lower in the first trimester, but

significantly higher in the second and third trimesters. Low concentration of PAPP-A in the first semester has also been reported to be associated with pregnancy complications[97,142]. The potential role of these placental proteins as a predictor of pre-eclampsia was assessed in a prospective cohort by Schneuer *et al.*[142]. Serum samples in the first trimester in combination with maternal characteristics (previous hypertension, parity, weight and age) and other biomarkers (β-hCG, PAPP-A) using multivariate models showed a moderate LR+ association for the prediction of early-onset pre-eclampsia.

Maternal characteristics with MAP

In a prospective screening study of 17,383 cases, Gallo *et al.* combined maternal characteristics (gestational age at screening, maternal weight and height, Afro-Caribbean racial origin, family history of pre-eclampsia, prior personal history of pre-eclampsia, cigarette smoking and chronic hypertension) with MAP measured in the first and second trimesters[98]. The model predicted pre-eclampsia with moderate test performance.

Maternal characteristics with biomarkers (serum PIGF and free β-hCG)

First trimester maternal serum PIGF, free β-hCG and maternal history were evaluated for the prediction of pre-eclampsia in a prospective cohort study of 2118 women[144]. Serum blood concentrations of PlGF and free β-hCG were quantified by DELFIA Xpress (Perkin Elmer) and adjusted for gestational age and maternal BMI. The multivariate model with serum PlGF, free β-hCG and chronic hypertension had a moderate LR+ for predicting early-onset pre-eclampsia.

Maternal characteristics with MAP and biomarkers (hyperglycosylated human chorionic gonadotrophin and PAPP-A)

A nested case–control study developed a regression model combining parity, MAP and first trimester hyperglycosylated hCG (hCG-h) and PAPP-A for the prediction of early-onset pre-eclampsia[145]. The study reported a moderate performance of the model for predicting the development of early-onset pre-eclampsia.

Maternal characteristics with MAP and biomarkers (taurine, PAPP-A, ADAM12 and PlGF)

Kuc *et al.* studied the utility of taurine, an amino acid which is involved in trophoblast invasion, the levels of which are altered at the time of disease with pre-eclampsia, in combination with MAP, maternal characteristics (parity, weight) and other biomarkers (PAPP-A, ADAM12 and PlGF) using a multiple logistic regression model[97]. Maternal serum samples were collected in the first trimester in 667 women in the nested case–control study. Early-onset pre-eclampsia with small-for-gestational age (SGA) was predicted moderately with the multivariate model with a strong LR-. A second model developed by in another case–control study showed moderate performance for the prediction of only early-onset pre-eclampsia[143].

Maternal characteristics with uterine artery PI

A review by Kleinrouweler *et al.* evaluated the value of adding second trimester uterine artery Doppler to patient characteristics in identification of nulliparous women at high risk for pre-eclampsia[111]. A logistic regression model combining blood pressure, uterine artery and bilateral uterine artery notching showed a good discriminatory predictive performance with an AUC of 0.85 (95% CI 0.67–1.00) in the study.

In another study, combining uterine artery PI expressed as $\log^{10}$ MoM and maternal characteristics (weight, height, race, parity and chronic hypertension) used in the early third trimester showed moderate association for predicting late-onset pre-eclampsia[146].

Maternal characteristics with blood pressure and uterine artery PI

Prediction of early onset pre-eclampsia in a prospective multicentre cohort study in 627 women was evaluated using demographic, clinical and ultrasound data in the first trimester[99]. The multivariate model included age, weight, systolic blood pressure, diastolic blood pressure and MAP at enrolment, parity, history of pre-eclampsia or hypertension, diabetes mellitus, log (uterine artery PI) and a history of preterm labour. The model

strongly predicted the development of early-onset pre-eclampsia in the development study. The performance of the model was moderate on external validation by Oliveira *et al.* in a prospective, observational study of 2669 women recruited in their first trimester[147].

Maternal characteristics with uterine artery Doppler and biomarkers (ADAM12 and PAPP-A)

In a prospective cohort study, Goetzinger *et al.* assessed the accuracy of a multivariate model combining first trimester bilateral uterine artery notching and PAPP-A, and maternal characteristics (chronic hypertension, history of pre-eclampsia, pre-gestational diabetes, obesity) for the prediction of pre-eclampsia[148]. The model was developed in one-half of a prospective cohort of 1200 patients in first trimester and validated in the second-half. The validated model had a moderate predictive accuracy for pre-eclampsia. It is worth mentioning that the split-half method of validation used has been reported to have some major drawbacks in prediction modelling.

Maternal characteristics with MAP and biomarkers (PlGF)

PlGF combined with MAP and maternal characteristics (a sister with a history of pre-eclampsia and a history of previous fertility treatment) were assessed for predictive accuracy for preterm pre-eclampsia in low-risk nulliparous women[149]. In the prospective multicentre cohort study, plasma PlGF was measured in second trimester using the triage assay. The model predicted pre-eclampsia with moderate performance.

Maternal characteristics with uterine artery PI and biomarkers (PlGF)

Serum concentrations of PlGF collected during the first, second and third trimesters of pregnancy and quantified using R&D were assessed in a case–control study of 541 women for the prediction of pre-eclampsia[150]. In a logistic regression model combining relative difference of PlGF from the first to the second trimester with BMI, second trimester uterine artery PI was a moderate predictor of pre-eclampsia.

Other multivariate studies

Circulating proteins and angiogenic factors

In a prospective study by Katsipi *et al.*, second trimester measurements of pulse wave velocity (PWV), which is a measure of aortic stiffness, was combined with serum levels of sFlt-1 in a regression model[151]. The model was a strong predictor of pre-eclampsia in high-risk pregnant women.

Park *et al.* assessed the predictive accuracy of the sFlt-1 : PlGF ratio (measured in the second and third trimesters (Roche Elecsys)) in combination with PAPP-A for late-onset pre-eclampsia in low risk women[90]. In this study, the third trimester sFlt-1 : PlGF ratio had a better predictive accuracy than the second trimester ratio and was a strong predictor of developing late-onset pre-eclampsia in low-risk women[90].

Myatt *et al.* combined first-trimester measurements of biomarkers (using Luminex assays[152]) with risk factors in an observational study in 2434 nulliparous women at low risk[137]. The best multivariable model included African-American race, systolic blood pressure, BMI, education level, ADAM-12, PAPP-A and PlGF, but performed poorly in predicting pre-eclampsia.

In a prospective cohort of 235 women, second-trimester uterine artery Doppler, serum biomarkers and lipid-related markers were evaluated for the prediction of pre-eclampsia[152]. The final model included maternal age, nulliparity, bilateral uterine artery notch, PlGF, sFlt-1, leptin and triglycerides, and was a poor predictor of pre-eclampsia in the high-risk cohort.

Histidine-rich glycoprotein (HRG), a multi-domain protein which has both pro- and anti-angiogenic properties, was studied as a predictor for preterm pre-eclampsia in combination with uterine artery pulsatility index (expressed as MoM) in a case–control study of 175 women[109]. The multivariate model showed a moderate LR- for predicting preterm pre-eclampsia.

In conclusion, most of the multivariate models combining maternal characteristics or biomarkers with other variables were either poor predictors of pre-eclampsia or did not give sufficient information to confirm the predictive ability of the test. Only a few seemed promising, especially those combining angiogenic factors with some other markers[151,155].

BEST PRACTICE POINTS

(Please see Appendix 5.5 for the evaluation of the strength of evidence.)

1. Women should be screened for clinical risk markers of pre-eclampsia from early pregnancy.
2. Consultation with an obstetrician or an obstetric internist/physician should be offered to women with a history of previous pre-eclampsia or another strong clinical marker of increased pre-eclampsia risk, particularly multiple pregnancy, antiphospholipid antibody syndrome, significant proteinuria at booking, or a pre-existing condition of hypertension, diabetes mellitus, or renal disease.
3. Screening for non-clinical risk markers cannot be recommended routinely at present for women at low or increased risk of pre-eclampsia until such screening has been shown to improve pregnancy outcome.

WHAT INTERNATIONAL GUIDELINES SAY (APPENDIX 5.4)

Abbreviations for Clinical Practice Guidelines are as follows ACOG (American College of Obstetricians and Gynecologists)[155], NICE (National Institutes of Clinical Excellence)[140], SOGC (Society of Obstetricians and Gynaecologists of Canada)[56,57], AOM (Association of Ontario Midwives)[156].

In a systematic review of international clinical practice guidelines on the hypertensive disorders of pregnancy[89], only three (ACOG, AOM, SOGC) out of 13 guidelines gave recommendations for the screening or prediction of pre-eclampsia or other hypertensive disorders of pregnancy. Well-established clinical risk markers such as medical history were the only recommended markers for screening. None of the guidelines recommended the use of ultrasonography or biomarkers; however, two guidelines (NICE, SOGC) suggested that a combination of these tests with clinical risk markers may be useful but require further studies to make sufficient conclusions.

SUMMARY

The ability to predict pre-eclampsia will facilitate early recognition of the disease, risk stratification and better management of these women to prevent associated severe complications, whilst making optimum use of limited resources[93,94]. In addition, predicting pre-eclampsia may provide more clarification of the pathogenesis and mechanisms involved in pre-eclampsia and might result in strategies for developing better prophylactic interventions and treatment[92]. There is need for large studies to validate the clinical value of these predictors and models before they can be applicable in clinical care for the prediction of pre-eclampsia.

PRIORITIES FOR FUTURE RESEARCH

Key priorities when conducting research on predicting pre-eclampsia include:

- Large prospective studies with adequate sample sizes as many of the studies reviewed in this chapter had small sample sizes with very low rates of pre-eclampsia.
- Studies reporting predictive accuracy according to disease onset and population risk will be beneficial in risk assessment and screening so as to allocate interventions to women who need them most. More focus should be targeted at predicting pre-eclampsia in the first trimester so that prophylactic interventions can be commenced.
- Standardisation of definitions and analytical methods will be useful for comparison and meta-analysis of results from prediction studies.
- Multivariate models need to be validated externally before they can be used in clinical practice. Only two studies among all the studies with multivariate models mentioned external validation[99,148]. Research has shown that the performance of a model can be overoptimistic when assessed in the same population used for building the model owing to overfitting[157,158]. Assessing the validity of these models in other population needs to be carried out to assure validity and reliability of predictive performance.
- There is a large knowledge deficit related to risk prediction for women in less-developed countries. An urgent priority is to diminish this deficit.

PRIORITIES IN UNDER-RESOURCED SETTINGS (TABLE 5.2)

Delays in disease identification and treatment are major contributing factors to the increased burden

Table 5.2 Priorities for prediction of hypertensive disorder of pregnancy in under-resourced settings

Antepartum and postpartum	
Initial priority	*Ultimate goal*
Early screening for pregnant women using risk factors and readily available predictive tests	Identification of high-risk women and initiation of preventative therapies
Cost-effectiveness studies for potential predictors	Use of cheap, point-of-care tests for early prediction
Recognition of recurrence risk factors based on prior pregnancy	Monitor and early treatment in future pregnancy

of the hypertensive disorders of pregnancy in LMICs[159]. Pre-eclampsia is a heterogeneous condition with different phenotypes. Future research is required to identify the risk factors and disease presentation for pre-eclampsia in low-income settings, which may differ from that in high-resourced settings, to allow for early interventions. Also, there might be need for earlier screening and initiation of preventative treatments in LMICs owing to the severity of outcomes in these settings.

A shortage of well-trained health professional and financial costs remain a significant risk burden for women in LMICs[160]. Therefore, for any predictive test to be beneficial in such settings, it should be a cheap, easy-to-use, point-of-care test that requires minimal training. Potential predictive tests that quickly measure angiogenic imbalance and glycosylated fibronectin during pregnancy are now available; however, further research is required to ascertain their use as a predictive tool.

Cost-effectiveness studies of these potential predictors are important especially for the LMICs which suffer most of the burden from pre-eclampsia[93]. An economic analysis of screening for pre-eclampsia using placenta markers (PP-13 and PlGF) and uterine artery Doppler compared with standard care has shown that screening for pre-eclampsia may be cost-effective[161]. Though the feasibility of uptake of this screening in a LMIC setting has not been studied, it represents a possible area of future research[162–169].

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