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REVIEW

First-trimester maternal factors and biomarker screening for preeclampsia

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ABSTRACT

Preeclampsia (PE), which affects about 2% of pregnancies, is a major cause of maternal and perinatal morbidity and mortality. PE can be subdivided into early onset PE with delivery <34 weeks' gestation and late onset PE with delivery ≥34 weeks. Early onset PE is associated with a higher incidence of adverse outcome. This review illustrates that effective screening for the development of early onset PE can be provided in the first-trimester of pregnancy. Screening by a combination of maternal risk factors, mean arterial pressure, uterine artery Doppler, maternal serum pregnancy-associated plasma protein-A and placental growth factor can identify about 95% of cases of early onset PE for a false-positive rate of 10%. © 2014 John Wiley & Sons, Ltd.

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INTRODUCTION

Preeclampsia (PE) is a major cause of maternal and perinatal morbidity and mortality and is thought to be predominantly as the consequence of impaired placentation.[1–3] There is extensive evidence that the risk of adverse outcome in relation to PE is much higher when the disease is severe and of early onset requiring delivery before 34 weeks' gestation, than at term.[4–7] A major challenge in modern obstetrics is early identification of pregnancies at high risk of early onset PE and undertaking the necessary measures to improve placentation and reduce the prevalence of the disease.

Extensive research in the last 20 years, mainly as a consequence of the shift in screening for aneuploidies from the second to the first-trimester of pregnancy, has identified a series of early biophysical and biochemical markers of impaired placentation.[8,9]

A combination of maternal demographic characteristics, including medical and obstetric history, uterine artery pulsatility index (PI), mean arterial pressure (MAP) and maternal serum pregnancy-associated plasma protein-A (PAPP-A) and placental growth factor (PlGF) at 11–13 weeks' gestation can identify a high proportion of pregnancies at high-risk for early onset PE.[8,9] The performance of the different methods of screening for PE is summarised in Table 1.

SCREENING BY MATERNAL HISTORY

Several professional bodies have issued guidelines on routine antenatal care recommending that at the booking visit, a woman's level of risk for PE, based on factors in her history, should be determined and women at increased risk are advised to take low-dose aspirin daily from early pregnancy until the birth of the baby (Table 2).[10–13] However, there are no available data on the performance of such recommended screening strategy, which essentially treats each of the risk factors as separate screening tests with additive detection rates (DRs) and false-positive rates (FPRs), and the effectiveness of early administration of low-dose aspirin in this at risk group following such screening.

It has been demonstrated that maternal demographic characteristics, including medical and obstetric history (Table 2), are potentially useful in screening for PE only when the various factors are incorporated into a combined algorithm derived by multivariate analysis.[14] With this approach to screening, the effects of variables are expressed as odds ratios for early onset, late onset or total PE. In general, the maternal risk factor profiles vary between early onset PE and late onset PE. This has led to the view that early and late PE may be different diseases, with the former being associated with a higher incidence of foetal growth restriction and both short-term and long-term maternal mortality and morbidity.[4–7] An alternative working hypothesis is that PE is a spectrum disorder the severity of which is reflected in gestational age at the time of delivery. Multivariate screening for PE with maternal risk factors has since evolved into a new approach in which the gestation at the time of delivery for PE is treated as a continuous rather than a categorical variable.[8] This approach, which is based on a survival time model, assumes that if the pregnancy was to continue indefinitely, all women would develop PE and

Table 1 Estimated detection rates (95% confidence intervals) of preeclampsia requiring delivery before 34, 37 and 42 weeks' gestation, at false positive rates of 5 and 10%[8,9]

		Detection rate (%) (95% CI)		
Screening test	FPR (%)	PE < 34 week	PE <37 week	PE <42 week
Maternal characteristics	5	36 (30–43)	33 (29–37)	29 (27–32)
	10	51 (44–57)	43 (39–47)	40 (38–43)
PAPP-A	5	44 (37–50)	37 (33–41)	32 (29–34)
	10	55 (48–61)	48 (44–52)	42 (40–45)
PlGF	5	59 (53–66)	41 (37–45)	29 (27–32)
	10	72 (66–78)	54 (50–59)	40 (38–43)
PAPP-A and PlGF	5	60 (54–67)	43(39–47)	30 (28–33)
	10	74 (68–30)	56 (52–60)	41 (38–43)
MAP	5	58 (52–65)	44 (40–48)	37 (35–40)
	10	73 (67–78)	59 (55–63)	54 (51–56)
Ut-PI	5	59 (53–66)	40 (36–44)	31 (29–34)
	10	75 (69–81)	55 (51–59)	42 (40–45)
MAP and Ut-PI	5	80 (74–85)	55 (51–59)	35 (33–37)
	10	90 (85–93)	72 (68–75)	57 (54–59)
MAP, Ut-PI and PAPP-A	5	82 (76–86)	53 (48–57)	36 (34–39)
	10	93 (88–95)	75 (71–78)	57 (54–59)
MAP, Ut-PI and PlGF	5	87 (82–91)	61 (57–65)	38 (35–40)
	10	96 (92–98)	77 (74–81)	53 (50–56)
MAP, Ut-PI, PAPP-A and PlGF	5	93 (89–96)	61 (57–65)	38 (35–40)
	10	96 (93–98)	77 (73–80)	54 (51–56)

PE, preeclampsia; FPR, false positive rate; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; MAP, mean arterial pressure; Ut-PI, uterine artery pulsatility index.

whether they do so or not before a specified gestational age depends on a competition between delivery before or after development of PE.[8] In this new approach (Figure 1), the effect of various risk factors is to modify the mean of the distribution of gestational age at delivery with PE. In pregnancies at low risk for PE, the gestational age distribution is shifted to the right with the implication that in most pregnancies, delivery will actually occur before the development of PE. In high-risk pregnancies, the distribution is shifted to the left, and the smaller the mean gestational age, the higher is the risk for PE.

In this competing risk model, the mean gestational age for delivery with PE is 55 weeks with estimated standard deviation of 7 weeks. Certain variables, including advancing maternal age over 35 years, increasing weight, Afro-Caribbean and South Asian racial origin, previous pregnancy with PE, conception by *in-vitro* fertilisation (IVF) and a medical history of chronic hypertension, pre-existing diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome, increase the risk for development of PE. The consequence of this increased risk is a shift to the left of the Gaussian distribution of the gestational age at delivery with PE (Figure 2). Estimated DR of PE requiring delivery before 34, 37 and 42 weeks' gestation in screening by maternal factors are about 36, 33 and 29%, respectively, at FPR of 5%, and 51, 43 and 40%, respectively, at FPR of 10% (Table 1).

SCREENING BY MATERNAL BIOCHEMICAL MARKERS

A large number of biochemical markers have been investigated for the prediction of PE (Table 3). Many such markers represent measurable manifestations of impaired placentation due to inadequate trophoblastic invasion of the maternal spiral arteries and reduced placental perfusion leading to placental ischaemia-related damage with the release of inflammatory factors, platelet activation, endothelial dysfunction, maternal renal dysfunction or abnormal oxidative stress.[15–21] Maternal serum PAPP-A and PlGF are two biochemical markers that have been investigated extensively and have shown promising results in the early prediction of PE. They have both been shown to be useful in screening for aneuploidies at 11–13 weeks' gestation, and they are now part of the platform of automated machines that provide reproducible results within 30–40 min of sampling.[22]

Pregnancy-associated plasma protein-A is a syncytiotrophoblast-derived metalloproteinase, which enhances the mitogenic function of the insulin-like growth factors by cleaving the complex formed between such growth factors and their binding proteins.[23,24] The insulin-like growth factor system is believed to play an important role in placental growth and development; it is therefore not surprising that low serum PAPP-A is associated with a higher incidence of PE. Increased level of maternal serum PAPP-A has been observed in established PE.[25–27] In chromosomally normal pregnancies,

Table 2 **Maternal risk factors for preeclampsia**

National Institute for Health and Care Excellence[10]
High-risk factors (one)
Hypertensive disease during a previous pregnancy
Chronic kidney disease
Autoimmune disease such as systemic lupus erythematosis or antiphospholipid syndrome
Type 1 or type 2 diabetes
Chronic hypertension
Moderate-risk factors (more than one)
First pregnancy
Age 40 years or older
Pregnancy interval of more than 10 years
BMI of 35 kg/m^2 or more at first visit
Family history of PE
Multiple pregnancy
World Health Organization[11]
Risk factors
Previous PE
Diabetes
Chronic hypertension
Renal disease
Autoimmune disease
Multiple pregnancy
The Society of Obstetricians and Gynaecologists of Canada[12]
High-risk factors (one)
Previous PE
Antiphospholipid antibodies
Pre-existing medical condition – hypertension, renal disease, and diabetes mellitus
Maternal age greater than 40 years
Obesity (BMI greater than 35 kg/m^2)
Family history of PE (mother or sister)
First ongoing pregnancy
Inter-pregnancy interval of more than 10 years
Booking systolic blood pressure > 130 mmHg or diastolic blood pressure > 80 mmHg
Multiple pregnancy
Moderate-risk factors (more than one)
Ethnicity – Nordic, Black, South Asian or Pacific Island
Lower socioeconomic status
Non-smoking
Heritable thrombophilias
Increased pre-pregnancy triglycerides
Family history of early onset cardiovascular disease
Cocaine and methamphetamine use
Inter-pregnancy interval of less than 2 years
Reproductive technologies
New partner
Gestational trophoblastic disease
Excessive weight gain in pregnancy
Infection during pregnancy
American College of Obstetricians and Gynecologists[13]
Risk factors
Previous early onset PE and preterm delivery at < 34 weeks' gestation
PE in more than one prior pregnancy

(Continues)

Table 2 **(Continued)**

BMI, body mass index; PE, preeclampsia.

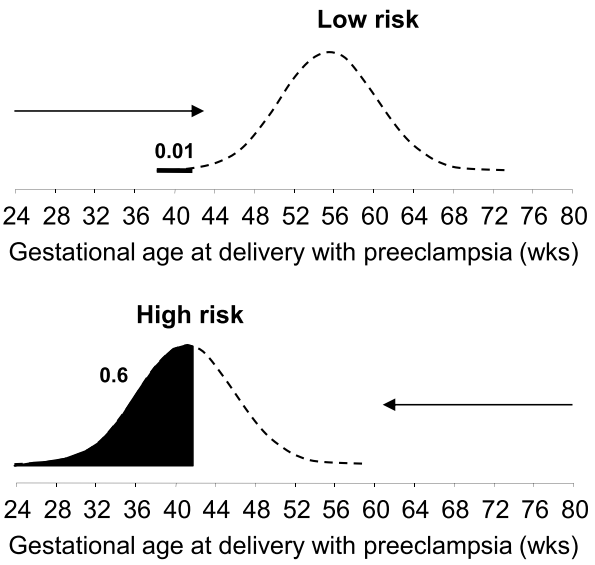

Figure 1 **Distribution of gestational age at delivery for preeclampsia. In pregnancies at low risk for PE, the gestational age distribution is shifted to the right, and in most pregnancies, delivery will occur before the development of PE. In pregnancies at high risk for PE, the distribution is shifted to the left. The risk of PE occurring at or before a specified gestational age is given by the area under the distribution curve (black). In the low-risk group, the risk of PE at or before 34 weeks' gestation is 0.01 or 1%, and in the high-risk group, the risk is 0.6 or 60%**

there is evidence that low maternal serum PAPP-A in the first- and second-trimesters is associated with increased risk for subsequent development of PE. However, measurement of PAPP-A alone is not an effective method of screening for PE because only 8–23% of affected cases have serum levels below the fifth percentile, which is about 0.4 MoM. At the fifth percentile of normal for PAPP-A, the reported odds ratios for PE varied between 1.5 and 4.6.[28–34]

Placental growth factor is a glycosylated dimeric glycoprotein, which is a member of the vascular endothelial growth factor sub-family. PlGF is synthesised in villous and extravillous cytotrophoblast and has both vasculogenetic and angiogenetic functions. It is believed to contribute a change in angiogenesis from a branching to a non-branching phenotype controlling the expansion of the capillary network. Its angiogenetic abilities

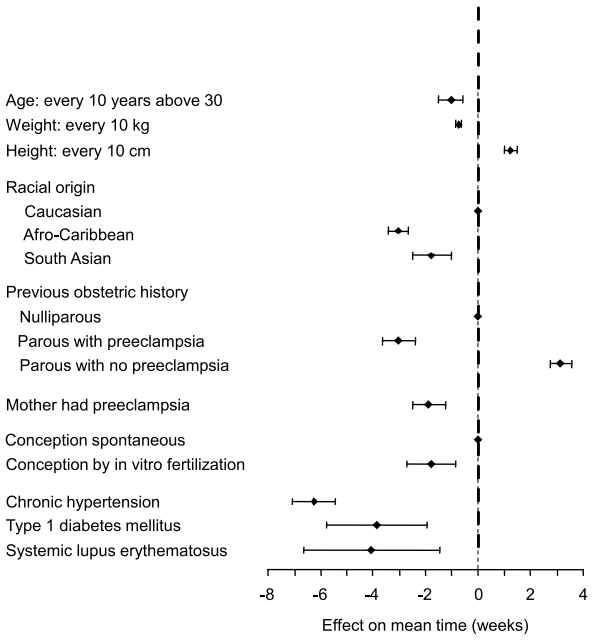

Figure 2 **Effects of maternal characteristics (with 95% confidence intervals) on the gestational age at delivery for preeclampsia. This effect is expressed as gestational weeks by which the expected gestational age at delivery for preeclampsia is altered**

have been speculated to play a role in normal pregnancy, and changes in the levels of PlGF or its inhibitory receptor have been implicated in the development of PE.[35–38] PE is associated with reduced placental production of PlGF, and several studies reported that during the clinical phase of PE, the maternal serum PlGF concentration is reduced. These reduced levels of serum PlGF precede the clinical onset of the disease and are evident from both the first- and second-trimesters of pregnancy.[39–47]

In biochemical testing, it is necessary to make adjustments in the measured maternal serum metabolite concentration to correct for certain maternal and pregnancy characteristics as well as the machine and reagents used for the assays, and the serum metabolite concentration is then expressed in a multiple of the expected median (MoM) of the normal.[48] First-trimester maternal serum concentrations of PAPP-A and PlGF have shown to be affected by gestational age at screening, maternal weight, racial origin, cigarette smoking, conception by IVF, nulliparity and pre-existing diabetes mellitus.[48,49] In addition, serum PlGF is also affected by maternal age.[49] Consequently, the measured concentrations of PAPP-A and PlGF must be adjusted for these variables before comparing results with pathological pregnancies. The MoM values of PAPP-A and PlGF are significantly reduced at 11–13 weeks' gestation in women who subsequently develop PE. There is a significant positive linear correlation between the MoM values of these biochemical markers with gestational age at delivery.[9] This observation further confirms that PE is a single pathophysiological entity with a wide spectrum of severity manifested in gestational age at which delivery becomes necessary for maternal and or foetal indications.

Table 3 **Proposed maternal biochemical markers for the prediction of preeclampsia**

A disintegrin and metalloprotease 12 (ADAM12)	L-arginine
Activin-A	L-homoarginine
Adiponectin	Leptin
Adrenomedullin	Magnesium
Alpha fetoprotein	Matrix metalloproteinase-9
Alpha-1-microglobulin	Microalbuminuria
Ang-2 angiopoietin-2	Microtransferrinuria
Antiphospholipid antibodies	N-acetyl-β-glucosaminidase
Antithrombin III	Neurokinin B
Atrial natriuretic peptide	Neuropeptide Y
Beta2-microglobulin	Neutrophil gelatinase-associated lipocalin
C-reactive protein	P-selectin
Calcium	Pentraxin 3
Cellular adhesion molecules	Placenta growth factor
Circulating trophoblast	Placental protein 13
Corticotropin release hormone	Plasminogen activator inhibitor-2
Cytokines	Platelet activation
Dimethylarginine (ADMA)	Platelet count
Endothelin	Pregnancy associated plasma protein-A
Estriol	Prostacyclin
Ferritin	Relaxin
Foetal DNA	Resistin
Foetal RNA	Serum lipids
Free foetal haemoglobin	Soluble endoglin
Fibronectin	Soluble fms-like tyrosine kinase
Genetic markers	Thromboxane
Haptoglobin	Thyroid function
Haematocrit	Total proteins
Homocysteine	Transferrin
Human chorionic gonadotropin	Tumour necrosis factor receptor-1
Human placental growth hormone	Uric acid
Inhibin A	Urinary calcium to creatinine ratio
Insulin-like growth factor	Urinary kallikrein
Insulin-like growth factor binding protein	Vascular endothelial growth factor
Insulin resistance	Visfatin
Isoprostanes	Vitamin D

Estimated DR of PE, at FPR of 5 and 10% in screening by maternal factors with biochemical markers are given in Table 1. The addition of maternal serum PAPP-A and PlGF to maternal factors improves the DR from 36 to 60% and 33 to 43%, at FPR of 5%, and from 51 to 74% and 43 to 56%, at FPR of 10%, for PE requiring delivery before 34 and 37 weeks' gestation, respectively, but not for PE delivering before 42 weeks.

SCREENING BY MATERNAL BIOPHYSICAL MARKERS

Blood pressure

In PE, hypertension develops as a result of vasoconstriction and reduced peripheral vascular compliance.[50] Although hypertension is only a secondary sign of PE, it is an important sign as it is an early indication of the disease. This highlights the importance of accurate monitoring of blood pressure (BP) during antenatal care. Accurate assessment of BP has been hindered by the considerable variability that BP exhibits within each individual. During BP measurement at rest, the first recording is often the highest recording, which decreases as the patients become more familiar with the procedure.[51] It is therefore recommended by professional bodies that a series of BP measurements should be made until a pre-specified level of stability is achieved.[52,53] In current clinical practice, the use of mercury sphygmomanometers remains the gold standard for non-invasive BP monitoring, but there are concerns for both the clinical performance and safety of these instruments.[54–56] Observer error is a major limitation of the auscultatory method, and terminal digit preference is perhaps the most common manifestation of suboptimal BP determination.[57] Other considerations include the rate of cuff deflation, the use of correct size cuff, the inter-arm difference in BP, and the arm position and posture that are recognised to have significant effects on BP determination.[52,53]

The introduction of automated BP monitoring allows simple, standardised and repeated measurements to be taken. It also addresses many of the errors associated with the conventional sphygmomanometer, but their use still requires the selection of the correct cuff size and proper patient positioning if accurate BPs are to be obtained. It has therefore been proposed that MAP should be measured by validated automated devices, with women in sitting position with back supported and legs uncrossed; that two measurements should be taken from each arm simultaneously with each arm supported at the level of the heart; and that the average of the four measurements should be used.[51,58]

There is substantial evidence demonstrating that an increase in BP in women destined to develop PE can be observed in the first- and second- trimesters of pregnancy.[59–93] Previous studies reported widely contradictory results in the performance of screening (DR, median 43%, range 5–100%; FPR, median 16%, range 0–66%) as a consequence of major methodological differences. The data from these studies, including more than 60 000 women with 3300 cases of PE, were compiled into a systematic review, which concluded that the MAP is significantly better than systolic or diastolic BP in predicting PE.[94]

The same principle for correcting biochemical markers for certain maternal characteristics and gestation should be applied to biophysical markers. First-trimester MAP has been shown to be affected by maternal weight, height, age, racial origin, cigarette smoking, family and prior history of PE and history of chronic hypertension, and consequently, it should be expressed as MoM after adjustment for these factors.[8] The MAP MoM is significantly increased at 11–13 weeks' gestation in women who subsequently develop PE, and there is a significant negative linear correlation between the MAP MoM with gestational age at delivery.[8] Estimated DR of PE, at FPRs of 5 and 10% in screening by maternal factors with MAP are given in Table 1. The addition of MAP to maternal factors improves the DR from 36 to 58%, 33 to 44% and 29 to 37%, at FPR of 5%, and from 51 to 73%, 43 to 59% and 40 to 54%, at FPR of 10%, for PE requiring delivery before 34, 37 and 42 weeks' gestation, respectively.

Uterine artery Doppler

The spiral arteries undergo a series of morphological changes during normal pregnancy.[20,95] This vascular transformation in the uterus is necessary to ensure a dramatic increase in blood supply to the intervillous space. The underlying mechanism for the development of PE is thought to be impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-muscular channels.[15–17,19,21] Doppler ultrasound provides a non-invasive method for the assessment of the uteroplacental circulation. The finding that impaired placental perfusion, reflected in increased uterine artery PI, is associated with the development of PE is compatible with the hypothesis that PE is the consequence of impaired placentation and the results of previous first and second-trimester Doppler studies as well as histological studies of the maternal spiral arteries.[96–99] Pathological studies have demonstrated that the prevalence of placental lesions in women with PE is inversely related to the gestation at delivery.[100,101]

The ability to achieve a reliable measurement of uterine artery PI is dependent on appropriate training of sonographers, adherence to a standard ultrasound technique to achieve uniformity of results among different operators. With the use of transabdominal ultrasonography, a sagittal section of the uterus should be obtained, and the cervical canal and internal cervical os are identified. Subsequently, the transducer is gently tilted from side to side, and color flow mapping is used to identify each uterine artery along the side of the cervix and uterus at the level of the internal os. Pulsed wave Doppler is then used with the sampling gate set at 2 mm to cover the whole vessel and care should be taken to ensure that the angle of insonation is less than 30°. When three similar consecutive waveforms are obtained, the PI is measured, and the mean PI of the left and right arteries is calculated. It is important to ensure that the peak systolic velocity is greater than 60 cm/s to ensure the arcuate artery is not being sampled instead of the uterine artery.[99]

First-trimester uterine artery PI has been shown to be affected by gestational age at screening, maternal weight, racial origin and history of pre-existing diabetes mellitus, and consequently, it should be expressed as MoM after adjustment for these factors. The uterine artery PI MoM is significantly increased at 11–13 weeks' gestation in women who subsequently develop PE, and there is a significant negative linear correlation between the uterine artery PI MoM with gestational age at delivery.[8] Estimated DR of PE, at FPR of 5 and 10% in screening by maternal factors with uterine artery PI are given in Table 1. The addition of uterine artery PI to maternal factors improves the DR from 36 to 59% and 33 to

40%, at FPR of 5%, and from 51 to 75% and 43 to 55%, at FPR of 10%, for PE requiring delivery before 34 and 37 weeks' gestation, respectively, but not for PE delivering before 42 weeks.

There is a significant association between MAP and uterine artery PI in PE and unaffected pregnancies, and therefore, when combining the two biophysical markers in calculating the patient specific risk for PE, the correlation factors must be taken into consideration to avoid overestimating the contributions from each marker to provide accurate risk assessment for PE. Estimated DR of PE requiring delivery before 34, 37 and 42 weeks' gestation in screening by maternal factors and biophysical markers are 80, 55 and 35%, respectively, at FPR of 5%, and 90, 72 and 57%, respectively, at FPR of 10% (Table 1).

SCREENING BY MATERNAL BIOCHEMICAL AND BIOPHYSICAL MARKERS

Analogous to the effective first-trimester combined screening for aneuploidies, effective screening for PE can also be achieved by a combination of maternal factors, biochemical and biophysical markers. With the use of the competing risk model, the gestational age at the time of delivery for PE is treated as a continuous variable. As demonstrated by the MoM values of serum PAPP-A and PlGF, MAP and uterine artery PI in pregnancies with PE, the distribution with gestational age is linear. Consequently, PE is considered as a single pathophysiological condition with varying degree of severity as defined by the gestational age at delivery. The major advantage of this model, compared with the other published models,[102–104] is that it offers the option to clinicians and researchers to select their own gestational age cutoff to define the high-risk group that could potentially benefit from therapeutic interventions starting from the first-trimester of pregnancy.[105–107]

It is important to recognise that there are significant associations between all biochemical and biophysical markers in PE and unaffected pregnancies, and therefore, when combining the four markers in calculating the patient specific risk for PE, the correlation factors are taken into account to provide accurate risk assessment for PE. Estimated DR of PE requiring delivery before 34, 37 and 42 weeks' gestation in screening by maternal factors with biochemical and biophysical markers are 93, 61 and 38%, respectively, at FPR of 5%, and 96, 77 and 54%, respectively, at FPR of 10% (Table 1).

FIRST-TRIMESTER SCREENING FOLLOWED BY THIRD-TRIMESTER RISK ASSESSMENT

Effective screening for early onset PE can be achieved in the first-trimester of pregnancy, but late onset PE remains a significant challenge for effective prediction. We are therefore proposing a two-stage strategy for identification of pregnancies at risk of PE. The first stage, at 11–13 weeks, is primarily aimed at effective prediction of early onset PE because the prevalence of this condition can be potentially reduced substantially by the prophylactic use of low-dose aspirin started before 16 weeks' gestation.[105–107] The second stage, at 30–33 weeks, is aimed at effective prediction of PE requiring delivery at or after 34 weeks because close monitoring of such pregnancies for earlier diagnosis of the clinical signs of the disease could potentially improve perinatal outcome through prompt interventions as the administration of antihypertensive medication and timely delivery.[108]

A survival time model is being developed that combines maternal characteristics and history, biochemical and biophysical markers at 30–33 weeks' gestation to estimate the risk of developing PE requiring delivery within selected intervals from the time of screening. Preliminary results to date confirm that the *a priori* risk for PE depends on maternal characteristics and is increased with increasing maternal age and weight and in women of Afro-Caribbean and South Asian racial origin, in those with personal or family history of PE and in women with pre-existing chronic hypertension, diabetes mellitus and systemic lupus erythematosus or antiphospholipid syndrome.[109] The third-trimester MAP and uterine artery PI are affected by maternal characteristics and history, and the corrected measurements as expressed in MoM values are inversely related to the severity of the disease reflected in the gestational age at delivery. Screening for PE at 30–33 weeks' gestation by a combination of maternal factors, MAP and uterine artery PI can identify about 90% of cases developing PE and requiring delivery within the subsequent 4 weeks, at FPR of 5%.[109]

Preeclampsia is thought to be the consequence of an imbalance in angiogenic and anti-angiogenic proteins.[110] Recent studies have focused on the investigation of pregnancies presenting to specialist clinics with signs of hypertensive disorders with the aim of identifying the subgroup that will develop severe PE requiring delivery within the subsequent 1–4 weeks. In such high-risk pregnancies, measurement of serum PlGF or soluble fms-like tyrosine kinase-1 (sFlt-1) to PlGF ratio are highly accurate in identifying the target group.[111–116] We have demonstrated that serum PlGF decreases with gestational age and maternal weight and is higher in women of Afro-Caribbean and South Asian racial origin than in Caucasians, in parous than nulliparous women and in smokers than in non-smokers. Serum sFlt-1 increases with gestational age and maternal age and decreases with maternal weight; it is increased in women of Afro-Caribbean racial origin and in pregnancies conceived by IVF and is lower in parous than nulliparous women.[117] In pregnancies complicated by PE, compared with normal pregnancies, serum PlGF MoM is decreased, and sFlt-1 MoM is increased. Screening for PE at 30–33 weeks' gestation by a combination of maternal factors, PlGF and sFlt-1 can identify all cases developing PE and requiring delivery within the subsequent 4 weeks, at FPR of 5%.[117]

CONCLUSION

Effective screening for early onset PE can be achieved in the first-trimester of pregnancy with a DR of about 95% and a FPR of 10%. In a proposed new approach to prenatal care, the potential value of an integrated clinic at 11–13 weeks' gestation in which maternal characteristics and history are

combined with the results of a series of biophysical and biochemical markers to assess the risk for a wide range of pregnancy complications has been extensively documented.[118] In the context of PE, the primary aim of such clinic is to identify those cases that would potentially benefit from prophylactic pharmacological interventions to improve placentation; the value of early screening and treatment of the high-risk group with low-dose aspirin is the subject of an ongoing randomised multicentre European study.

It is likely that a similar integrated clinic at 30–33 weeks will emerge for effective prediction of pregnancy complications that develop during the third-trimester. The potential value of such a clinic is to improve perinatal outcome by rationalising and individualising the timing and content of subsequent visits for selection of the best time for delivery. Prospective studies are underway to confirm the predictive abilities of the biomarkers identified, both for early and late onset PE, as well as for other obstetric complications related to abnormal placentation, such as early and severe foetal growth restriction.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- It is unclear whether early and late onset preeclampsia are one disease or two different diseases.
- There are several maternal risk factors and first-trimester biomarkers that perform better for the prediction of early than late onset preeclampsia.
- The independent predictive value of these markers has been poorly studied.

WHAT DOES THIS STUDY ADD?

- Using multivariate analysis in a large study population, we have identified the independent predictive value of each obstetric, demographic and maternal serum marker.
- Mathematical modelling suggests high predictive ability at a reasonable false-positive rate; prospective studies are underway to confirm the predictive values.

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