Review Article

New directions in the prediction of pre-eclampsia

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Pre-eclampsia remains an important worldwide cause of maternal and perinatal morbidity and mortality. Improved prediction of those destined to develop this condition would allow for timely initiation of prophylactic therapy, appropriate antenatal surveillance and better targeted research into preventive interventions. This paper reviews recent research into strategies for the prediction of pre-eclampsia, including the use of maternal risk factors, mean maternal arterial pressure, ultrasound parameters and biomarkers. The most promising strategies involve multiparametric approaches, which use a variety of individual parameters in combination, as has been established in first-trimester aneuploidy screening. The paper concludes with a discussion of the issues around the introduction of such testing into clinical practice.

Key words: aspirin, blood pressure, mass screening, pre-eclampsia, pregnancy-induced hypertension.

Introduction

Pre-eclampsia – *de novo* proteinuric hypertension that develops after 20 weeks of gestation – is an important obstetric concern in Australia, with recent data from New South Wales identifying a mean incidence of 3.3% in singleton pregnancies,[1] in keeping with global estimates.[2] It remains a major cause of maternal and perinatal morbidity and mortality, both in Australia[3,4] and worldwide.[5] Furthermore, the onset of pre-eclampsia may not be predicted by maternal history and risk factors alone, especially in nulliparae.[6] Assessing its development is a primary focus of routine antenatal care and is responsible for many referrals to pregnancy day-stay units and antenatal admissions to hospital. As such, improving the prediction of pre-eclampsia has been the focus of a significant amount of research, both in asymptomatic populations at various gestations with varying *a priori* risk (ie screening), and for the prediction of the disease in patients in whom pre-eclampsia is suspected (ie diagnosis). This paper focuses on screening the performance of predictive tests for pre-eclampsia, the rationale for such tests and their integration into anticipated changes in early pregnancy management.

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The Rationale for Prediction

The criteria a condition must meet to justify screening are well established and have remained essentially unchanged since first proposed by Wilson and Jungner[7] in 1968; these criteria are listed in Table 1. Whether pre-eclampsia yet meets these criteria continues to be the subject of debate, particularly regarding the effectiveness of prophylactic interventions, the absence of an effective treatment for established disease other than delivery and the performance of currently available testing strategies.[8,9]

With respect to prevention, the benefit of aspirin in preventing pre-eclampsia among women at an increased risk of this condition has been the subject of a Cochrane review[10] (46 trials, 32,891 women), which found a relative risk of 0.83 (95% confidence interval 0.77–0.89), corresponding to a number needed to treat (NNT) of 72 to prevent one case of pre-eclampsia. Subsequently, the Perinatal Antiplatelet Review of International Studies (PARIS) collaborators published a meta-analysis of individual patient data[11] from 32,217 women, which identified a relative risk of 0.90 (95% confidence interval 0.84–0.97) and a number needed to treat of 114 (for a population in which 8% developed pre-eclampsia). Both studies also found statistically significant reductions in preterm birth.

Numerous studies have assessed the impact of the gestational age at which aspirin is commenced. A meta-analysis from 2010 found a relative risk of pre-eclampsia among high-risk women of 0.47 (95% confidence interval 0.34–0.65, NNT 9) when aspirin is started at 16 weeks or earlier; when started later, the benefit was not significant (relative risk 0.81, 95% confidence interval 0.63–1.03).[12]

Table 1 WHO principles of screening

Condition	The condition sought should be an important health problem
	There should be a recognisable latent or early symptomatic stage
	The natural history of the condition, including development from latent to declared disease, should be adequately understood
Test	There should be a suitable test or examination
	The test should be acceptable to the population
Treatment	There should be an accepted treatment for patients with recognised disease
Screening program	Facilities for diagnosis and treatment should be available
	There should be an agreed policy on whom to treat as patients
	The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole
	Case finding should be a continuing process and not a 'once and for all' project

For severe pre-eclampsia, the benefit is even more marked, with a meta-analysis published this year having found a relative risk of 0.18 (95% CI 0.08–0.41) with aspirin prior to 16 weeks, compared with a relative risk of 0.65 (95% CI 0.4–1.07) with later commencement of aspirin.[13] A similar benefit was identified in a smaller meta-analysis, limited to women whose increased risk of pre-eclampsia was determined by abnormal first-trimester uterine artery Doppler indices.[14] Use of aspirin in this group prior to 16 weeks of gestation was associated with a relative risk of 0.6 for pre-eclampsia (95% CI 0.37–0.83) and 0.3 for severe pre-eclampsia (95% CI 0.11–0.69). However, these subgroup meta-analyses have important limitations that may result in an overstatement of aspirin's benefit in early gestation: studies in the pre-16 week subgroup were small, very few were negative (suggesting publication bias), and there were significant systematic differences in the pre- and post-16 week subgroups (eg in the rate of pre-eclampsia in the control arms).[15] Indeed, neither the Cochrane review[10] nor the PARIS meta-analysis of individual patient data[11] found a difference in the benefit derived from aspirin if commenced before or after 20 weeks. Nevertheless, current concepts of abnormal placentation in the pathogenesis of pre-eclampsia are consistent with aspirin having a greater beneficial effect if commenced earlier in pregnancy; further research is needed to confirm and better define the magnitude of this benefit and thus the importance of early identification of high-risk patients.

The only other agent found to be of benefit in preventing pre-eclampsia is calcium, with a Cochrane review[16] identifying a relative risk of 0.45 (95% confidence interval 0.31–0.65) with calcium supplementation as against placebo (13 trials, 15,730 women). Women with low baseline calcium intake derive greater benefit (eight trials, 10,678 women: RR 0.36, 95% confidence interval 0.20–0.65), as do those at high risk (five trials, 587 women: RR 0.22, 95% CI 0.12–0.42).

No other interventions, pharmacological or otherwise, have yet been shown to prevent pre-eclampsia.[17] Numerous agents are under investigation, including low molecular weight heparin,[18] high-dose folate,[19] vitamin D[20] and statins.[21] Trials of these agents are being conducted in populations whose high risk of pre-eclampsia has been determined solely by past obstetric history and/or maternal factors. As demonstrated below, risk stratification by these means alone is poorly predictive of pre-eclampsia, and thus, the potential benefit of these agents in a truly high-risk population may not be identified. Establishing optimally specific and sensitive screening strategies to identify populations at highest risk of pre-eclampsia would improve the statistical and clinical validity of future trials involving these and other prophylactic agents.[22] Doing so would also allow for optimisation of the designated model and location of antenatal care. This is of particular relevance to the Australian context, with geography rendering access to tertiary- and even secondary-level care inconvenient and expensive for those living in regional and remote locations. Similarly, limited tertiary resources could thus be reserved for those likely to derive the greatest benefit, such as those at highest risk of early-onset pre-eclampsia.

Screening Strategies

Research on screening strategies for pre-eclampsia has varied in the modalities employed, the *a priori* risk of the target group, outcome stratification (early- or late-onset pre-eclampsia) and the gestational age at which screening is performed. No single screening test has been shown to adjust pre-existing maternal risk of pre-eclampsia with sufficient specificity and sensitivity to be of clinical use. As with aneuploidy screening, the best-performing tests involve multiple parameters in combination.[23]

Maternal factors

Published guidelines on the use of maternal factors and history in the ascertainment of risk of pre-eclampsia perform moderately well at best. A recent analysis[24] of the NICE[25] and PRECOG[26] guidelines (UK) found the former to have a sensitivity of 77% and specificity of 54% and a positive predictive value (PPV) of 7%, while the latter had a sensitivity of 59% and specificity of 81%, with a PPV of 11% (assuming a 4% incidence of pre-eclampsia). The NICE guidelines were further assessed in a prospective screening study,[6] in which they returned a detection rate of 89.2% for early-onset pre-eclampsia and 93% for late-onset disease, for a false-positive rate of 64.1%. The authors demonstrate that these same factors, when combined into an algorithm derived from multivariate analysis, yield a detection rate of 37%

for early-onset and 28.9% for late-onset pre-eclampsia, for a 5% false-positive rate. A prior history of pre-eclampsia is the most consistent predictive factor, which clearly cannot apply to nulliparas – the group with the highest incidence of this condition. The limitations of using maternal factors alone to predict pre-eclampsia in primigravidae were illustrated by the multicentre prospective SCOPE study, in which an algorithm was devised that detected 37% of pre-eclampsia for a 10% false-positive rate and 61% for a 25% false-positive rate (AUC of 0.76).[27]

Mean arterial pressure

The mean arterial pressure is calculated by dividing the sum of the systolic and twice the diastolic blood pressures by three and is thus easily measurable. A meta-analysis from 2008 found that mean arterial pressure (MAP) was more predictive of pre-eclampsia among low-risk women in the first or second trimester than either the systolic or diastolic readings alone.[28] For high-risk women, the diastolic blood pressure measured between 13 and 20 weeks of gestation was the parameter most predictive for pre-eclampsia (positive likelihood ratio 2.8). Subsequently, a prospective study in 5590 women with singleton pregnancies identified that a combination of maternal risk factors and MAP measured between 11 and 13+6 weeks of gestation was more predictive of pre-eclampsia (AUC 0.852) than either alone (AUC of 0.801 and 0.734, respectively).[29] Overall, for a false-positive rate of 10%, a combination of maternal history and MAP identified 62.5% of cases of pre-eclampsia. This combination remains the basis of all subsequently developed screening strategies; the importance of its contribution is highlighted by the poor performance of any strategy that relies solely on ultrasonographic and/or biochemical parameters.

Ultrasound parameters

The utility of Doppler analysis of the uterine artery in predicting pre-eclampsia has been extensively studied, initially in the mid-second trimester and more recently in early pregnancy. The abnormal placentation that characterises pre-eclampsia is associated with an increased resistance in the uteroplacental circulation. Ultrasonographic evidence of this resistance includes the presence of a diastolic 'notch' in the Doppler waveform of the uterine artery or an increase in that vessel's pulsatility index (PI).[30] Being an objectively measured continuous variable, the latter is preferable to the somewhat subjective assessment of 'notching'.[8]

Overall, the value of uterine artery Doppler analysis in predicting pre-eclampsia is poor; a meta-analysis published in 2008 confirmed that it performs better in the second than in the first trimester and is of maximal utility in identifying severe or early-onset pre-eclampsia: among low-risk women, an increased uterine artery PI in the second trimester has a sensitivity of 78% and specificity of 95% for detecting severe pre-eclampsia (positive likelihood ratio 15.6, negative 0.23).[31] More recently, a meta-analysis of 11 studies (43,122 women) found an overall sensitivity and specificity of first-trimester uterine artery Doppler in predicting pre-eclampsia of 26% (95% confidence interval 24–29) and 91% (95% CI 91–91).[32] It has been suggested that Doppler studies might be most predictive if performed in a sequential fashion in both the first and second trimesters.[33] However, such an approach would preclude the early initiation of prophylaxis.

Other potential ultrasonographic parameters for the prediction of pre-eclampsia include 3D power Doppler assessment of placental volume and vascularity,[34] maternal MCA Doppler indices[35] and maternal ophthalmic artery Doppler indices.[36] Further research will determine whether any of these is superior to uterine artery Doppler analysis.

Biomarkers

A wide range of potential biomarkers for pre-eclampsia has been identified in the maternal circulation, reflecting this condition's complex pathogenesis.[37] No single biomarker has demonstrated sufficient predictive value to be of clinical utility[38]; rather, they appear to be most valuable in combination with other parameters. A categorisation of the most promising biomarkers is as follows:

- Markers of *placental function* include pregnancy-associated plasma protein A (PAPP-A, routinely tested in first-trimester aneuploidy screening) and plasma protein 13 (PP-13), both of which are reduced in women who go on to develop pre-eclampsia.[39] PAPP-A is a protease that originates from the syncytiotrophoblast and may influence placentation through its effect on insulin-like growth factors.[40] PP-13 is also derived from the syncytiotrophoblast; it is thought to influence maternal artery remodelling and placental implantation.[41]
- Cystatin C is an established marker for renal function, increasing as the glomerular filtration rate falls.[42] It is also an inhibitor of cysteine proteases (cathepsins), which are important in normal trophoblastic invasion; both cathepsins and cystatin C are expressed in decidual macrophages and trophoblasts.[43] Increased serum levels of cystatin C in the first trimester are associated with the later development of pre-eclampsia.[44]
- The maternal *inflammatory response* in established pre-eclampsia results in increased levels of pentraxin 3 (PTX3), an inflammatory marker from the same molecular class as C-reactive protein.[45] Levels of PTX3 increase in normal pregnancy with advancing gestation[46]; they have also been shown to be higher in the first trimester of pregnancies, which subsequently develop early-onset pre-eclampsia (pre-34 weeks), but not in those with late pre-eclampsia or gestational hypertension.[47]

- *Angiogenic* agents include placental growth factor (PlGF) and vascular endothelial growth factor (VEGF); the former is easier to measure and has been found to be reduced in patients destined to develop pre-eclampsia.[48] Both are bound by soluble fms-like tyrosine kinase-1 (sFlt-1), thus limiting their interaction with endothelial cells. Assessment of this anti-angiogenic factor in the first trimester does not aid in the prediction of pre-eclampsia.[49] However, sFlt-1 works synergistically with soluble endoglin (sEng),[50,51] another anti-angiogenic factor, reduced levels of which in the late first trimester are associated with pre-eclampsia.[52]
- Inhibin A (assessed as part of second trimester maternal serum aneuploidy screening) and activin A are proteins of *placental origin*, which belong to the transforming growth factor (TGF-β) family; both have been shown to be increased prior to 14 weeks in pre-eclamptic pregnancies.[53,54] Cell-free *fetal DNA* is rapidly establishing its role in aneuploidy testing[55]; its levels increase with advancing gestation in normal pregnancies and to higher levels in pregnancies affected by pre-eclampsia.[56] A recent small retrospective case–control study of the predictive value of cell-free fetal DNA in the first trimester demonstrated a sensitivity and specificity of 100% for the development of pre-eclampsia[57]; prospective analysis will be required to determine the true utility of this technique.
- Maternal *endothelial dysfunction*, a characteristic feature of pre-eclampsia, results in an increased production of potential biomarkers for the disease. Neutrophil gelatinase-associated lipocalin (NGAL) is a glycoprotein found in neutrophil granules; it is increased in the first trimester of pregnancies later complicated by early- or late-onset pre-eclampsia.[58] P-selectin is a cell surface adhesion molecule expressed by endothelial cells and activated platelets. Given the platelet activation that occurs in pre-eclampsia,[59] its levels are increased when this disease is established[60] and also in the first trimester of such pregnancies.[55]

Multiparametric tests

In the last four years, multiparametric approaches have been described whose positive and negative likelihood ratios meet the desired thresholds for pre-eclampsia screening tests (commonly quoted as >10 and <0.1, respectively).[17] The first of these was developed by the Fetal Medicine Foundation (London), which utilised maternal factors, MAP, PAPP-A, PlGF and uterine artery Doppler, all measured in the first trimester.[61] In a series of 7797 women, for a false-positive rate of 5%, this approach returned an overall detection rate of 93.1% for early-onset pre-eclampsia. Consistent with previous research, the detection rates for late-onset pre-eclampsia (35.7%) and gestational hypertension (18.3%) were considerably lower. Investigators from the same institution have reported on the varying performance of a range of testing panels incorporating different parameters. For example, first-trimester screening combining maternal factors, uterine artery Doppler, MAP and PAPP-A demonstrated a detection rate for early pre-eclampsia of 83.8% at a 5% false-positive rate.[62] This same combination has been prospectively validated in a Spanish cohort of 5759 patients (80.8% detection rate of early PE for a 10% false-positive rate)[63] and in an Australian group (91.7% detection for a 10% FPR).[64]

Table 2 summarises a selection of the best-performing first-trimester multiparametric tests for the prediction of early pre-eclampsia. The test with the highest detection rate (DR) is based on a competing risks model incorporating maternal factors, uterine artery Doppler, MAP, PAPP-A and PlGF.[65] As is the case with aneuploidy screening, this model also provides risk cut-off levels (1:128 for a DR of 93.4% at a FPR of 5%, 1:269 for a DR of 96.3% at a FPR of 10%). Not surprisingly, sequential multiparametric testing has been found to be superior to testing in the first trimester alone; for example, measuring changes in PlGF, sEng and sFlt-1 between 6–15 weeks and 20–25 weeks has been found to have a sensitivity of 100% and specificity of 98% for early pre-eclampsia.[66] As noted earlier, the clinical utility of such testing is limited by the later gestation at which results are generated.

Future Directions

Early pregnancy screening for pre-eclampsia is not currently recommended by international health authorities, such as the UK National Screening Authority.[67] In the

Table 2 Characteristics of multiparametric tests for early-onset pre-eclampsia

Study	Parameters	Detection rate for 5% FPR	Detection rate for 10% FPR
Poon *et al.*[61]	MC, UtA Dopp, MAP, PlGF, PAPP-A	93%	
Poon *et al.*[62]	MC, UtA Dopp, MAP, PAPP-A	84%	95%
Akolekar *et al.*[72]	MC, UtA Dopp, MAP, PlGF, PAPP-A, PP-13, sEng, inhibin A, activin A, PTX3, P-selectin	91%	95%
Akolekar *et al.*[65]	MC, UtA Dopp, MAP, PlGF, PAPP-A	93%	96%
Scazzocchio *et al.*[63]	MC, UtA Dopp, MAP, PAPP-A	69%	81%

MC, maternal characteristics; UtA Dopp, uterine artery Doppler (usually PI); MAP, mean arterial pressure.

light of the evidence presented above, it is perhaps time for such recommendations to be reviewed. The improvement in the performance of pre-eclampsia screening strategies that include uterine artery Doppler and biomarker analysis (in addition to clinical risk factors and MAP) must be proportional to the increased costs associated with these tests, as must the benefits of early intervention for those who screen positive. Initial economic modelling elsewhere (eg in an Israeli centre[68]) would suggest a favourable cost-benefit ratio; such an assessment should be performed in the Australian context prior to the widespread introduction of screening, taking into consideration the significant proportion of patients who already have a 12-week ultrasound and biomarker assessment for first-trimester aneuploidy screening. The commercialisation of tests for certain biomarkers (eg the DELFIA® Xpress PlGF kit; PerkinElmer Inc., Waltham, MA, USA) will inevitably lead to their clinical availability; their introduction would ideally be integrated into a multiparametric screening test with maximal (and clearly established) sensitivity and specificity. Management of patients identified to be at high risk of pre-eclampsia should be in accordance with evidence-based consensus guidelines, and the performance of the screening test could be monitored by an ongoing audit of pregnancy outcomes. The evolution of multiparametric testing in the aneuploidy screening programme provides valuable lessons for pre-eclampsia screening, including the importance of establishing *a priori* risk, expressing markers as multiples of the gestation-specific median and adjusting markers for covariables – although highlighting their differences is equally important.[69] A high-risk aneuploidy screen result leads to invasive diagnostic testing being offered, which carries a 0.5–1% chance of pregnancy loss. Conversely, patients screened as at high risk of pre-eclampsia would be offered prophylactic therapy (of negligible risk of harm) and enhanced surveillance – interventions that are already commonly offered to those whose increased risk has been sub optimally determined by history and risk factors alone. Clearly, future prophylactic therapies of proven benefit may carry greater risks of harm, to which the specificity of the screening test would need to be proportional.

The potential harm to those who receive a false-negative screening result for pre-eclampsia is likely to be limited to the detriment of not being prescribed prophylactic therapy, as existing schedules of antenatal care would continue to facilitate the identification of signs of pre-eclampsia. Although screening for hypertension (and, in some institutions, proteinuria) is a key aspect of antenatal care in the second and third trimesters, other aspects need to be addressed as well, such as screening for growth restriction, diabetes and group B streptococcus, provision of childbirth education and administration of Rh(D) immunoglobulin where required. A low-risk early screening test for pre-eclampsia (whether true or false) has little or no bearing on these other components of antenatal care, thereby ensuring that pregnant women will continue to have opportunities for the identification of hypertension. This is in contrast to those who receive a false-negative aneuploidy screening result, for whom the chromosomal anomaly will generally only be apparent following delivery.

Finally, the advent of cell-free fetal DNA testing in maternal plasma will revolutionise current approaches to aneuploidy screening.[70] At the same time, the utility of the 12-week ultrasound and various biomarkers in identifying fetal anomalies and predicting other pregnancy complications (eg gestational diabetes, preterm birth and fetal growth restriction) is actively being studied.[71] As a consequence, the next decade is likely to see a paradigm shift in early pregnancy screening, which will require substantial changes to current models of antenatal care, particularly in the public system.

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