Circulating biomarker use for the prediction and detection of pre-eclampsia

Pre-eclampsia is a major cause of maternal and perinatal mortality. Scientific advances in recent decades have meant new possibilities for enhancing the prediction and diagnosis of pre-eclampsia. Here we detail current biomarker-based approaches under development or validated for clinical translation that will revolutionize obstetric practice in the years ahead.

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Pre-eclampsia

Pre-eclampsia affects 3–8% of all pregnancies and is a major cause of maternal and perinatal morbidity and mortality. Globally, pre-eclampsia is responsible for over 60 000 maternal deaths and greater than 500 000 neonatal deaths every year. It is a heterogeneous condition, likely having multiple underlying etiologies, producing a clinical syndrome typically characterized by maternal hypertension and multi-organ dysfunction, including fetoplacental, renal, hepatic, hematological and/or neurological dysfunction. Currently, the mainstay of treatment is delivery, with delivery of the placenta curing the condition. Although this is a reasonable option when the disease presents at term (37–42 weeks gestation), when pre-eclampsia arises prematurely delivery places the neonate at the significant risks of prematurity. As such, current medical approaches for preterm pre-eclampsia, especially if occurring <34 weeks gestation, are centred around close observation of both maternal and fetal well-being, aiming to prolong gestation towards term, but timing delivery to minimize risks for mother and child due to evolving pre-eclampsia. On average this approach will only see a gestational advancement of 7–14 days [1]. Therefore, these women often require care in highly specialized obstetric units with access to a neonatal intensive care unit. The ability to predict those women most at risk of developing pre-eclampsia, may afford the opportunity to commence preventative therapies, such as aspirin, but may also enable better allocation of healthcare models.

Pre-eclampsia had long been considered to solely be of concern during the time of pregnancy; however, it is now appreciated that it is also associated with negative long-term health implications for the mother and child. Women who had pre-eclampsia are at increased risk of cardiovascular disease and death in the decades that follow [2]. Similarly, children born from pregnancies affected by pre-eclampsia are also at greater risk of hypertension later in life [3]. As such, it is becoming increasingly important to accurately diagnose pre-eclampsia and provide ongoing long-term healthcare following birth to minimize the morbidity.

The pathophysiology of pre-eclampsia

Multiple phenotypes of pre-eclampsia exist. Currently, these are understood to be early-onset and late-onset forms of pre-eclampsia. Underlying abnormal placentation is a key component of early-onset disease, where the shallowly implanted placenta leads to ischemia-reperfusion injuries within the placenta. This impacts on placental gene expression leading to an upregulation of hypoxia-regulated genes including anti-angiogenic proteins, such as soluble fms-like tyrosine kinase 1 (sFLT-1) and soluble endoglin. sFLT-1, a soluble version of the vascular endothelial growth factor receptor 1, is able to bind and antagonize the actions of the angiogenic proteins, vascular endothelial growth factor (VEGF) and placental growth factor (PIGF). These proteins are essential in maintaining endothelial homeostasis and a reduction in their bioavailability produces the widespread end-organ endothelial dysfunction that yields the clinical pre-eclamptic phenotype.

In comparison, late-onset pre-eclampsia is thought to result from pre-existing endothelial dysfunction, such as exists in women with chronic hypertension, obesity and diabetes. In normal pregnancy, sFLT-1 within the maternal circulation gradually rises across gestation. In women with pre-existing endothelial dysfunction, this normal rise in sFLT-1 will lead to a worsening of endothelial function, which may tip the balance towards the clinical development of term pre-eclampsia.

With the discovery of sFLT-1 in 2003 [4], pre-eclampsia research has been firmly focused both on better prediction and diagnosis of the disease, but also the development of therapeutics. The use of anti-angiogenic and angiogenic biomarkers for pre-eclampsia is now entering into clinical use or in the process of translation to improve prediction and diagnosis across pregnancy.

Predicting pre-eclampsia during the first trimester

First-trimester screening for fetal aneuploidy is the most commonly employed test in early gestation for the prediction of later pregnancy complications, namely, delivery of an infant with a chromosomal anomaly. The principles underpinning these multiparametric tests have informed the development of screening strategies using multiple biomarkers in early gestation for the prediction of other complications, such as pre-eclampsia [5].

In 2009, researchers from the Fetal Medicine Foundation (FMF; UK) evaluated a multiparametric test incorporating maternal factors, mean arterial pressure, uterine artery Doppler pulsatility index, circulating PIGF, and PAPP-A. It detected 93% of early-onset pre-eclampsia with a false positive rate (FPR) of 5% [6]. This approach has subsequently been externally validated
producing similar rates of detection for early-onset pre-eclampsia (80.8–91.7%), but with a 10% FPR [7, 8].

Very recently, a prospective multicentre study of first-trimester screening for pre-eclampsia in singleton pregnancies was published [9]. The study population had 239 (2.7%) cases that developed pre-eclampsia, including 17 (0.2%), 59 (0.7%) and 180 (2.0%) at <32, <37 and >37 weeks, respectively. Using combined screening by maternal factors, mean arterial pressure, uterine artery pulsatility index and serum PlGF the detection rate was 100% (95% CI 80–100) for pre-eclampsia at <32 weeks, 75% (95% CI 62–85) at <37 weeks and 43% (95% CI 35–50) at >37 weeks, with a 10% FPR. As such, The FMF model is the most accurate and thoroughly validated algorithm available at 11–13 weeks to predict pre-eclampsia in a low-risk population.

A clear benefit to predicting women at high risk of pre-eclampsia in the first trimester is the opportunity it affords to institute preventative therapies. Currently, low dose aspirin is the only medication that appears to reduce the rate of pre-eclampsia in high-risk women, with the results of the ASPRE study (Aspirin for evidence-based PRE-eclampsia prevention) [10], a European multicentre randomized controlled trial, eagerly awaited to define how effective preventative aspirin truly is. This trial applied the FMF screening model in 30 000 women at 11–13 weeks gestation, with those at increased risk of pre-eclampsia randomly assigned to aspirin (n=798) or placebo (n=822). However, the FMF algorithm cannot detect all cases of preterm pre-eclampsia and detection of term disease was poor, furthermore, aspirin cannot prevent all cases. Thus, further studies with novel biomarkers to improve screening (especially for term pre-eclampsia) and new treatments are needed to reduce the global burden of this disease.

Predicting pre-eclampsia later in pregnancy
Circulating anti-angiogenic factor levels are often below the detection limit of available assays during the first trimester; however, both sFLT-1 and soluble endoglin levels rise as gestation advances and are significantly raised in the maternal circulation, while PI GF levels are significantly reduced, weeks before the clinical development of pre-eclampsia [11, 12]. These findings have prompted widespread study into the use of these biomarkers in predictive algorithms for pre-eclampsia. PI GF appears the most useful biomarker in first-trimester screening, as well as in the second trimester either on its own or in a ratio with sFLT-1. Automated systems able to rapidly process these biomarkers are already available and the utility of PI GF and sFLT-1 has now been assessed in multiple trials. PI GF appears the most accurate biomarker, capable of detecting approximately 75% of women who will develop early-onset pre-eclampsia [13], whereas the sFLT-1:PI GF ratio...
appears to perform well as a negative predictor of early-onset pre-eclampsia [14].

Recently, an assay able to detect a placental-specific variant of sFLT-1, known as sFLT-1 e15a, has been developed [15]. This may provide improved positive predictive performance in predicting who will develop pre-eclampsia. As anticipated, total sFLT-1 and sFLT-1 e15a, are most useful in predicting early-onset disease [16], in which abnormal placental pathology is central to disease development. However, measurement in the third trimester and assessing the longitudinal change in expression may be useful for the prediction of late-onset pre-eclampsia [17]. Certainly, total sFLT-1, as well as PI GF and maternal factors currently appear the most promising for predicting term disease; however, none have been validated or perform favourably enough for translation to clinical practice [18].

Improving the diagnosis of pre-eclampsia

The use of angiogenic and anti-angiogenic biomarkers may provide significant improvement for the accurate diagnosis of pre-eclampsia itself. Current markers used to diagnose pre-eclampsia consist of a history of pre-eclamptic symptoms (such as headache, visual disturbance or epigastric pain), physical signs (such as high blood pressure, hyper-reflexia or tender liver edge) and biochemical markers (such as proteinuria; elevated liver transaminases, uric acid or creatinine; or thrombocyto-penia). However, these can also be present in other pre-existing medical conditions, such as renal disease, which can make the accurate diagnosis of pre-eclampsia a challenge.

PI GF currently appears the most promising biomarker for improving the accurate diagnosis of pre-eclampsia, even in the setting of pre-existing renal disease or chronic hypertension [19]. PI GF outperforms our current diagnostic approach for pre-eclampsia, particularly for disease occurring <35 weeks gestation. However, the challenge remains to find an accurate diagnostic test to identify late-onset pre-eclampsia and improve test performance to minimize the FPR.

Conclusion

The last 15 years has seen a rapid increase in our knowledge of the pre-eclamptic process enabling development of promising new approaches to disease prediction and diagnosis. However, the pathway to translation of these tests into widespread clinical use has been slowed by the heterogeneity of pre-eclampsia itself, as it is likely that no one test or approach will work for all forms of pre-eclampsia. New approaches and ongoing progress in our understanding of the disease process provide hope that our clinical approach to pre-eclampsia will change significantly in the years ahead, hopefully to the betterment of the women and infants we care for.

References


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