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Review

Preterm pre-eclampsia: What every neonatologist should know

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ABSTRACT

Although pre-eclampsia affects 5–10% of pregnancies globally and is responsible for substantial maternal and perinatal morbidity and mortality, currently there is no cure other than delivery of the baby. Predictive screening tests based on clinical risk factors, with or without the addition of biomarkers and imaging, have been developed, but adoption into clinical practice is limited by suboptimal test performance. Once established pre-eclampsia is diagnosed, a woman is usually managed expectantly prior to 37 weeks' gestation to reduce perinatal morbidity and mortality associated with iatrogenic prematurity until maternal or fetal triggers for delivery mean that risks of pregnancy prolongation outweigh the benefits. Associated fetal growth restriction is a common feature of pre-eclampsia, particularly with early-onset disease, and will influence decisions for delivery and subsequent neonatal course. Prematurity and fetal growth restriction both have potential short and long-term consequences for the infant and child.

1. Introduction

The decision for iatrogenic preterm delivery of a baby is never straightforward. Prematurity can be associated with considerable mortality and morbidity involving multiple organ systems particularly at gestations prior to 32 weeks. Very preterm birth is associated with an increased incidence of multisystem pathology encompassing bronchopulmonary dysplasia, neurodevelopmental sequelae including cerebral palsy and gastrointestinal disorders such as necrotizing enterocolitis [1]. However, where there are substantial concerns regarding the maternal or fetal condition, these risks may be outweighed by the immediate threat to the life of the mother or baby and preterm delivery becomes unavoidable.

Pre-eclampsia is a pregnancy-specific, multisystem syndrome that can pose such a clinical dilemma, as delivery of the fetus and placenta is currently the only definitive treatment. The condition is characterised by new onset hypertension in the mother (defined as systolic blood pressure $\geq$ 140 mm Hg and/or diastolic blood pressure $\geq$ 90 mm Hg) after 20 weeks' gestation together with other features of maternal disease (proteinuria, thrombocytopenia, deranged liver or renal function, pulmonary oedema or cerebral complications) or fetal growth restriction [2]. Maternal and fetal manifestations represent a clinical spectrum ranging from mild hypertension and proteinuria in the mother with an appropriately grown fetus near term to early-onset disease causing severe complications including eclampsia and pulmonary oedema in the mother and severe growth restriction in the fetus.

If disease onset is early, expectant management with careful control of blood pressure and monitoring of fetal wellbeing is possible but iatrogenic preterm delivery is still often warranted. Prolongation of the pregnancy at early gestations is purely to confer benefit for the fetus and reduce complications associated with prematurity as definitive treatment remains delivery of the baby. This review discusses the implications of pre-eclampsia from the perspective of the health of the fetus, with regards to prevention, management and long-term consequences.

2. Pathophysiology

Although extensive research into the pathophysiology of pre-eclampsia has been undertaken, the exact mechanisms remain uncertain and are likely to be multifactorial. Pre-eclampsia is usually characterised by abnormal placentation. In normal pregnancy, the villous cytotrophoblast invades into the inner third of the myometrium and the maternal spiral arteries are converted into low resistance vessels by loss of their endothelium and muscle fibres. In pre-eclampsia, the invasion of cytotrophoblast cells into the maternal spiral arteries does not occur to the same extent. Hypo-perfusion of the fetoplacental unit and associated hypoxia results in the release of reactive oxygen species and cytokines from the placenta that lead to endothelial dysfunction and inflammation, together with the downstream clinical manifestations of the disease which usually become apparent in the third (or less frequently the late second) trimester.

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Alterations in both innate and adaptive immune processes may also be implicated in the pathophysiology of the disease and a genetic predisposition to pre-eclampsia may result from polymorphisms in genes such as those encoding inflammatory modulators which are activated by placental insufficiency or hypoxia resulting in alteration of transcriptional function of downstream cytokines or anti-angiogenic proteins [3].

Research over recent decades has characterised an imbalance of circulating angiogenic and antiangiogenic factors [4] including increased concentrations of anti-angiogenic proteins soluble endoglin and soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased concentrations of the pro-angiogenic vascular endothelial growth factor and placental growth factor (PlGF). It remains unclear the extent to which this imbalance is a cause or consequence of the rest of the disease process [3].

3. Risk factors and screening for pre-eclampsia

Although there is a good understanding of the risk factors for pre-eclampsia, this has not yet translated into a widely adopted screening test, as these currently have limited performance for introduction into clinical practice. For the neonatologist, this is relevant for two reasons as it provides an understanding of the possible comorbidities associated with the disease, and an appreciation of why introduction of a screening test has been elusive.

A recent systematic review and meta-analysis of early pregnancy clinical risk factors reported that those most strongly associated with a high rate of pre-eclampsia include antiphospholipid antibody syndrome (pooled incidence 17.3%, 95% confidence interval 6.8% to 31.4%), chronic hypertension (16.0%, 12.6% to 19.7%), prior pre-eclampsia (12.0%, 10.4% to 13.7%) and pre-gestational diabetes (11.0%, 8.4% to 13.8%. [5] However, the population attributable fraction (i.e. the proportional reduction in population disease or mortality that would occur if exposure to a risk factor were reduced to ideal) showed that different risk factors contributed most: nulliparity (32.3%, 27.4% to 37.0%), pre-pregnancy body mass index > 25 (23.8%, 22.0% to 25.6%) and prior pre-eclampsia (22.8%, 19.6% to 26.3%). These need to be interpreted, though, in the light of those risk factors that are modifiable (e.g. raised body mass index) and those that are not (e.g. nulliparity).

A woman with pre-eclampsia may have one of a number of co-morbidities that are relevant to the fetus and newborn (e.g. diabetes) and that in addition, these may make identification of complications such as fetal growth restriction more challenging if the co-existent diseases drive fetal growth in opposing directions. Identification of these risk factors has informed current screening within the National Institute for Health and Care Excellence guidelines [6] for management of Hypertension in Pregnancy (Table 1).

However, the recognition that screening through clinical risk factors alone is imperfect has led other groups to explore the incorporation of additional biomarker-based tests and/or sonographic imaging of the maternal vasculature, particularly uterine artery Doppler flow velocity waveforms. Over 70 risk prediction models have been published and systematically reviewed, but internal and external validations of these models have been limited, hampering demonstration of adequate performance sufficient for recommendation into clinical practice by a national guideline body. This largely reflects the challenge of predicting a disease as heterogeneous as described above; screening tests have better performance for early onset pre-eclampsia with associated fetal growth restriction, where placentation is impaired, abnormal placental biomarkers and/or flow velocity waveforms to the placenta can be identified and the interval between a screening test (e.g. at 12 or 22 weeks of pregnancy) and onset of the disease is short. Prediction of late onset pre-eclampsia (e.g. developing after 37 weeks' gestation) remains elusive.

Table 1
Screening for pre-eclampsia based on clinical risk factors [22].

	Risk factor
One or more risk factors present	Chronic kidney disease
	Autoimmune disease
	Type 1 or type 2 diabetes
	Chronic hypertension
	Hypertensive disease during a previous pregnancy
Two or more risk factors present	First pregnancy
	Age ≥ 40 years
	Pregnancy interval > 10 years
	BMI ≥ 35 kg/m^2
	Family history of pre-eclampsia
	Multi-fetal (e.g. twin) pregnancy

Screening tests that incorporate serum biomarkers such as placental growth factor, pregnancy associated plasma protein A (PAPP-A), uterine artery pulsatility index and multiple maternal clinical risk factors have reported detection rates of 54% for all pre-eclampsia cases, and 96% of those requiring delivery before 34 weeks' gestation [7]. This screening algorithm has been validated by the same group in other populations [8,9] but test performance has often diminished when applied by other researchers into different populations (reviewed by Kane [10]) usually due to overfitting of the model highlighting discrepancies between the cohort in whom the model was developed and the 'real-world' environment.

Although a comparison of clinical risk factors and multi-parameter screening tests has reported enhanced performance of the latter, identifying 75% of women with pre-eclampsia requiring delivery before 37 weeks (compared to 39% with clinical risk factors alone) [11], adoption by national screening committees has not yet occurred in the UK or the US, particularly related to concern over the high false-positive rate associated with such screening tests.

4. Prevention of pre-eclampsia

The main purpose of screening is to enable prophylactic treatment to be given (either in clinical practice or within a research setting), and/or appropriate surveillance for higher-risk women. Development of preventative treatments has continued over recent decades. The only treatment with a high-quality evidence base for demonstrating benefit is the administration of low-dose aspirin from the second trimester. One of its proposed mechanisms of action is by inhibition of thromboxane A2 synthesis (increased in women who develop pre-eclampsia) resulting in vasodilation and improved blood flow and implantation. In individual patient data meta-analyses, low dose aspirin has been shown to have a moderate effect in reducing the relative risk (0.90 95% CI 0.84–0.97) of pre-eclampsia [12].

More recently, work has indicated a dose-response relationship up to 150 mg of aspirin, with higher doses potentially conferring increased benefit for early onset disease [13]. The recent ASPRE trial confirmed that this higher dose of aspirin was associated with a marked reduction in preterm pre-eclampsia (odds ratio 0.38; 95% CI 0.20 to 0.74) [9] but concerns have been expressed over remaining uncertainty over the effect on perinatal and other safety outcomes. Other innovative therapies are currently being evaluated, based on the pathophysiological pathways identified in pre-eclampsia, including alpha-1-microglobulin, recombinant antithrombin, angiogenic factors and proton pump inhibitors [14]; although several are being trialled, none are close to introduction to routine clinical practice. The challenges of drug development in pregnancy including regulatory hurdles have been detailed elsewhere [15] and continue to present a major obstacle to the introduction of novel prophylactic treatments.