Placental syndromes: getting to the heart of the matter

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Human placentation is uniquely associated with physiological remodeling of the spiral arteries, where deep placentation involves almost complete transformation of maternal spiral arteries. Defective deep placentation has been associated with the development of preeclampsia and fetal growth restriction - collectively termed placental syndromes – complicating some 10-15% of pregnancies (1). The clinical significance of PE and FGR and their deleterious effect on maternal, fetal and neonatal health are well accepted. This editorial attempts to highlight the importance of maternal hemodynamics and their relevance to placental syndromes.

Implied causation of placental syndromes

Conventional beliefs

A placenta is essential for the diseases to occur, and is therefore believed to be central in the pathogenesis of PE and FGR. Furthermore, the cure for PE is delivery of the placenta, supporting the crucial role of the placenta. The name 'placental syndrome' itself demonstrates the commonly accepted belief that the association between inadequate trophoblast invasion and the subsequent development of PE and/or FGR is causal in nature. Incomplete remodeling of uterine spiral arteries is thought to result in a placental 'stress' biochemical response, which can lead to the subsequent development of both FGR and endothelial cell dysfunction characteristic of PE.

Placental histology

A number of characteristic histological lesions have been associated with the development of both PE and FGR – especially in early or preterm gestations. Although several studies consistently demonstrate that these lesions occur more frequently in case of FGR and PE, the vast majority of cases of PE and FGR occur at term, where placental histology is predominantly normal (2). Furthermore, even though these characteristic histological placental lesions are more prevalent in pathological pregnancies, the overall incidence is higher in placentas from normal pregnancies because they outnumber pathological pregnancies by several-fold. Importantly, the only lesions consistently seen more often in PE and FGR pregnancies at term are those associated with maternal under perfusion of the placenta, such as massive perivillous fibrin deposition (3).

Birthweight

An expected and anticipated consequence of poor placental development is impaired fetal growth, and consistent with this, about 60% of early-onset PE cases exhibit FGR. However,

over 80% of PE cases occur at term and the majority of the neonates in these pregnancies are of normal size with a slightly higher prevalence of both smaller and even larger than average weight neonates (4). Normal and larger birthweights are not consistent with long-standing placental dysfunction.

Placental biomarkers

First trimester serum levels of pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PlGF) are reduced in pregnancies destined to develop preterm FGR and PE. In the studies with the best-reported screening performance for a 5% false positive rate, the sensitivity for early-onset PE using PlGF was around 60%, falling to approximately 15% for term PE (5). These hormonal patterns support the placental origins hypothesis of early-onset PE, but not for late PE. In the later stages of pregnancy, an imbalance of vasoactive angiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and placental growth factor (PlGF) are thought to adversely affect vascular homeostasis and contribute to the development of PE signs and symptoms (6). These angiogenic factors were first recognized for their involvement in the development of cardiovascular disorder in the non-pregnant state.

Uterine artery Doppler

Uterine artery Doppler assessment in the first trimester has been shown to have good sensitivity and specificity of 47.8% and 92.1% respectively for the detection of early-onset PE (7). Increased uterine artery resistance indices have long been presumed to be the consequence of incomplete trophoblast invasion of maternal spiral arteries resulting in a high-resistance placental circulation and under-perfused fetoplacental unit. However, the finding that ophthalmic artery Doppler assessment in pregnancy is equally effective as uterine artery assessment in screening for FGR and/or PE suggests that maternal Doppler assessments are reflecting maternal cardiovascular performance rather than trophoblast development (8). The reduced sensitivity of uterine artery Doppler indices for late-onset PE lends further support to the argument that the heterogeneity observed in PE, is due to early onset PE being related to a dysfunctional placenta, whilst late onset PE may have to be explained by an alternative, possibly cardiovascular etiology. Corroborative evidence for this hypothesis is provided by MRI studies showing that early PE is associated with lower placental perfusion fractions compared to gestation-matched controls. In contrast, late PE had larger placental perfusion fractions supporting the argument that late-onset PE is unlikely to be due to placental insufficiency (9).

Genetics of placental syndromes

Familial clustering has been observed and reported in PE and therefore supports a genetic causality link. Many susceptibility genes for PE have been reported in the literature, however the function of the majority of these genetic loci remains unknown. The few PE genetic loci with known associations have previously been implicated in adult cardiovascular disease, suggesting shared genetic link between PE and cardiovascular disease (10).

Maternal cardiovascular adaptation

Whilst we have continued to firmly believe that the placenta is a central pre-requisite and therefore crucial to the development of PE for many decades, as highlighted above, there

are inconsistencies in the placental origins hypothesis and the role of the maternal cardiovascular system should be evaluated. If we consider gestational diabetes as an analogous condition, where the placenta is required for its development, characteristic placental lesions are seen, fetal growth is affected and the condition is cured by interruption of pregnancy. In spite of these parallels with PE, gestational diabetes is not considered a placental disorder, and it is well accepted that the endocrine 'stress' of pregnancy results in the development of gestational diabetes when maternal pancreatic function is sub-optimal.

Magnitude of maternal cardiovascular adaptation

If similarities exist between so called placental syndromes and gestational diabetes, then pregnancy will need to present a significant strain on the maternal cardiovascular system. Indeed, studies have demonstrated that normal pregnancy results in an excessive increase in left ventricular mass, adverse ventricular remodeling and even overt diastolic dysfunction in a proportion of apparently healthy women at term (11, 12). These changes are an order of magnitude greater than observed in elite athletes and some pathological conditions in non-pregnant individuals.

Evidence of cardiovascular maladaptation

At diagnosis there is evidence of impaired myocardial relaxation and diastolic dysfunction in PE, and to a lesser extent, in FGR. Mild-moderate left ventricular diastolic dysfunction is seen in approximately half of women with early onset PE, with one in five women having biventricular systolic dysfunction. This impairment in cardiac function is likely to be related to increase in cardiac afterload (high systemic vascular resistance) and abnormal left ventricular remodeling/hypertrophy (13, 14). The abnormal pattern of remodeling observed in PE is similar to that observed in non-pregnant individuals with essential hypertension and is consistent with an impairment that is afterload-induced.

Risk factors for cardiovascular maladaptation

Both PE and FGR have predisposing clinical risk factors such as increased maternal age, ethnic origin, increased body mass index (BMI), diabetes and other maternal co-morbidities. The similarities in these predisposing risk factors have been taken to imply a deleterious impact on trophoblast development. However, it is important to acknowledge that these risk factors have long been associated with the development of cardiovascular disease in the non-pregnant population (15).

Late uteroplacental dysfunction

A recent large, population-based study demonstrated a 2% increase in risk of term SGA infants for every 1mm Hg increase in maternal blood pressure within the normotensive range (16). The authors suggested that the observed maternal pre-hypertension is a response to impaired placental function - but consideration should be given to the possibility that the placenta is a perfusion-dependent organ and that impaired cardiovascular function may cause placental dysfunction, rather than the other way round (17, 18). In support of the latter hypothesis previous work has demonstrated maternal ventricular remodeling and diastolic function as well as significantly poorer placental perfusion in normotensive FGR pregnancies (19). This is supported by the characteristic histological findings of placental hypoperfusion in cases of FGR. This evidence suggests that term FGR may well occur as a consequence of secondary placental dysfunction caused by impaired maternal cardiovascular function. This is in contrast to that of preterm fetal

growth restriction, in which placental cause is unchallenged, and implies that both impaired maternal perfusion of the placenta (an extrinsic defect) and impaired placental development (an intrinsic defect) may lead to FGR.

Post-partum cardiovascular legacy

The parallels between placental syndromes and gestational diabetes can also be extended into the post-partum period. Women whose pregnancies were complicated by gestational diabetes have a 50% risk of developing diabetes in the subsequent decade. Similarly, women whose pregnancies were complicated with PE and FGR are predisposed to increased post-partum cardiovascular morbidity and mortality including chronic hypertension, myocardial infarction, heart failure, stroke and death (20). In fact, even in apparently healthy women, postpartum follow-up after pregnancies complicated by placental syndromes have demonstrated persistent remodeling and left ventricular dysfunction (21). Population studies have suggested that the association of PE with adverse cardiovascular outcome postpartum may be due largely to shared pre-pregnancy risk factors rather than reflecting a direct influence of PE (22).

Clinical relevance of maternal hemodynamics

The belief that the placenta causes PE and FGR has been championed for several decades. Although this is almost certainly true for the minority of cases that constitute early-onset disorders, consistent and emerging evidence suggests otherwise for the development of late-onset PE and FGR. The inconsistencies and discrepancies with the placental origins hypothesis have been attributed to heterogeneity or explained as the maternal form of the disorders. Neither one of these is adequate nor actual explanations of the causality of PE and FGR at term. A stronger argument can be made for the role of the maternal cardiovascular system in the development of PE and FGR. The evidence cited here and within this issue of the Journal supports maternal cardiovascular involvement in the etiology of placental syndromes - especially the late-onset variety. Whilst intrinsic placental dysfunction and the subsequent maladaptation of the maternal cardiovascular system leads to early-onset PE and FGR, late-onset disorders are more likely to be associated with an acquired placental dysfunction as a result of the maternal heart not being able to meet the excessive hemodynamic and metabolic demands of an advanced or overgrown pregnancy. Both the intrinsic and acquired placental dysfunction results in placental stress and result in the cluster of maternal signs and symptoms we recognize as PE and/or FGR. Forming a better understanding of the precise etiology of placental syndromes is critical for the development of accurate diagnostic aids, improved screening, better triage by disease severity and offering targeted preventative and therapeutic measures. It is possible that the lack of progress in improving outcomes of placental syndromes may be linked to the inaccurate assignment of disease causality in PE and FGR. The advent of a research dealing with maternal hemodynamic alteration in pregnancy will be critical to further progress in this arena.

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