Long-Term Consequences of Placental Disease

By Michelle Hladunewich

About 5 percent of pregnancies suffer complications from abnormal placental development. The process of placentation begins when blastocysts adhere to the uterine endometrium, forming a lineage of epithelial cells termed the invasive extravillous cytotrophoblast, which then invades the uterine wall to create the decidua, transforming the spiral arteries into a low-resistance uteroplacental circulation.

Impaired development of the uteroplacental vasculature, therefore, has its origins in the first trimester as a result of an abnormal interaction between the invading extravillous cytotrophoblast and the maternal immune system, resulting in decidual vasculopathy, with small, poorly developed spiral arteries. As these pregnancies progress, placental ischemia and infarction may result in a maternal placental syndrome—pre-eclampsia, placental abruption, and/or the ensuing adverse perinatal outcomes, including fetal growth restriction and stillbirth.

It was previously thought that the consequences of maternal placental disease resolved quickly and completely after delivery of the placenta. More recently, however, it has become clear that placental disease, as a major basis of the maternal placental syndrome, is a marker of future vascular disease, forecasting a vastly different health trajectory than that of a woman who has had normal placental function and a healthy pregnancy.

Epidemiology

The first study to describe the relationship between pre-eclampsia and cardiovascular disease used the Norwegian Medical Birth Registry (1). Although this study did not show an increased risk of death among women with pre-eclampsia who were delivered at term, it did show almost a three-fold increased risk of death and an eightfold increased risk of cardiovascular death in women who were delivered before 37 weeks, interpreted as a surrogate marker for more severe disease.

An increased risk of cardiovascular death was also noted among women with preterm delivery but without clinical pre-eclampsia. This highlights a key component to understanding which women are at risk for future vascular disease, inasmuch as a third of preterm deliveries are caused by placental implantation abnormalities. These findings have been confirmed and expanded by other studies in which, in addition to an increased risk of cardiovascular disease, an increased risk of cerebrovascular disease, peripheral vascular disease, and end stage renal disease was also noted (2, 3).

In the Cardiovascular Health after Maternal Placental Syndromes study, the importance of placental vascular disease in long-term maternal outcome was again highlighted, inasmuch as the worst survival was noted in women with pre-eclampsia accompanied by fetal death (2). The societal effect of this increased vascular risk, however, is best demonstrated by the Child Health and Development Cohort. Data from over 14,000 women with an average of 30 years of follow-up noted the median age for cardiovascular events to be 56 years, with a cumulative survival of 86 percent for women with early-onset pre-eclampsia compared with 98 percent for those with late-onset pre-eclampsia and 99 percent for those with healthy pregnancies (4).

Pathophysiology

Whether damage to the vascular endothelium secondary to maternal placental syndrome results in an increased risk of future vascular disease, or whether pre-existing factors underlie both the predisposition to placental disease and the later development of vascular disease, is unknown. Studies, however, are noting common genetic and physiologic links and, therefore, shared risk factors between pre-eclampsia and cardiovascular disease.

There are several examples of common genetic pathways. Catechol-*O*-methyltransferase (COMT) is responsible for the degradation of both estrogens and catecholamines. Mice deficient in COMT, and hence 2-methoxyestradiol (2ME), have abnormal placentation and develop a phenotype that resembles human pre-eclampsia (5). In a mouse model of cardiovascular disease, 2ME treatment can decrease atherosclerosis by 52 percent and cholesterol by 19 percent (6). Human data have also emerged for this shared genetic factor. A nested case-control study assessed the three common haplotypes of the central region of the COMT gene wherein the haplotype translates into COMT activity. The haplotype associated with low COMT activity was noted in 7 percent of the population and was associated with recurrent pre-eclampsia (7).

In other studies attempting to determine a relationship of haplotype to coronary artery disease, low COMT activity was associated with worse coronary outcomes, interacting with higher homocysteine levels (8). The T235 allele, an angiotensinogen gene polymorphism, has been noted in women with abnormal spiral artery modeling (9). The ACOX2 gene polymorphism was studied in the decidua basalis tissue of women with pre-eclampsia and was noted to be downregulated and inversely correlated to triglyceride levels (10). Finally, homozygotes for the nitric oxide synthetase gene polymorphism ASP298 had significantly lower flow-mediated vasodilatation than those homozygous for the GLU298 polymorphism at 12 weeks gestation, and this may prove important in the vascular adaptation to pregnancy (11). Such genetic polymorphisms have been noted to also contribute to hypertension, coronary artery disease, and even chronic kidney disease in other populations.

Examples also exist of shared physiologic processes. There is significant evidence to suggest that alterations in the renin-angiotensin system (RAS) play a significant role in the pathogenesis of pre-eclampsia. In normal pregnancy, the RAS regulates blood pressure and volume status. Because the placenta has no autonomic innervation, it relies on angiotensin to regulate vascular resistance. Although components of RAS have been demonstrated to be upregulated in normal pregnancy, vascular insensitivity to angiotensin II (AngII) infusions has been demonstrated in healthy pregnant women, and AngII sensitivity is a demonstrated predictor for the development of pre-eclampsia (12).

A potential mechanism for enhanced sensitivity is the presence of an immunoglobulin G autoantibody to the AT1 receptor identified in the serum of women with pre-eclampsia (13). Alternatively, upregulation of the AT1 receptor on the decidual, or maternal, side of the placenta has also been demonstrated (14). Such a maternal abnormality could result in abnormal placentation as well as future cardiovascular disease. Furthermore, abnormalities in angiotensin sensitivity have been shown to remain into the postpartum period. In a recent study, women with a history of pre-eclampsia were noted to have salt-sensitive hypertension, and in the salt-deprived state—a state wherein the RAS is maximally stimulated—there was evidence of increased angiotensin sensitivity with respect to both aldosterone release and blood pressure response to AngII infusion (15).

There seems little doubt that the vascular endothelial cell is the primary target of maternal placental syndromes and is intimately involved in the future pathogenesis of vascular disease. Flow-mediated vasodilation (FMD) is a well accepted physiologic measure of endothelial dysfunction that has been demonstrated to be associated with long-term adverse vascular consequences. Endothelial-dependent vasodilation is impaired in women with pre-eclampsia compared with healthy gravid control individuals. Furthermore, there appears to be an association with uterine artery Doppler assessment, given that the highest rates of impaired FMD were noted in patients who also had abnormal uterine artery flow (16).

Recent studies have also demonstrated impaired endothelial-dependent, but not endothelial-independent, vasodilation in the forearm vasculature months after delivery in women with a history of maternal placental disease that cannot be explained by adjustment for traditional cardiovascular risk factors. In a recent study wherein the maternal phenotype was carefully classified, endothelial dysfunction, as determined by impaired FMD, was observed in 93 percent and 89 percent of women with early-onset pre-eclampsia (≤34 weeks gestation) and isolated intrauterine growth rate (fetal growth below the fifth centile without evidence of maternal disease), respectively, compared with 22 percent of women with late-onset pre-eclampsia—a value that did not differ significantly from that in a control population (17). Moreover, the findings appeared to be driven by fetal growth restriction, paralleling the epidemiologic literature and highlighting the importance of assessing future vascular risk on the basis of placental pathology.

The recent discovery of endothelial progenitor cells (EPCs) suggests that vascular repair and angiogenesis constitute a dynamic process that extends well beyond the embryonic phase, modulated by numerous identified and as yet undiscovered cardiovascular risk factors. Endothelial progenitor cells may mediate the noted differences in endothelial dysfunction between women with or without pre-eclampsia, and they are established in the cardiovascular literature as biomarkers of vascular disease. In women with maternal placental syndrome manifest as pre-eclampsia, EPCs are decreased, with increased rates of cellular senescence (18). As measured by standard flow cytometry, EPCs have been demonstrated to be significantly decreased in a small group of women with pre-eclampsia as compared with healthy control individuals in the third trimester (19).

With both shared genetic and physiologic pathways between maternal placental and cardiovascular disease, one might also expect shared risk factors. A recent study that combined data from two large population-based studies with medical birth registry data identified 3225 singleton births with a prepregnancy cardiovascular risk assessment (20). When adjustment was made for traditional cardiovascular risk factors, including body mass index, blood pressure, and cholesterol in the women who developed pre-eclampsia during pregnancy, much of the risk for future vascular disease could be accounted for, suggesting that women programmed to develop vascular disease also get placental vascular disease and that both cardiometabolic and endothelial dysfunction likely predate and persist after pregnancy.

Summary Statements

Maternal placental disease is now regarded as a female-specific risk factor for future morbidity and mortality caused by vascular disease. Future studies will continue to identify common pathways and potential treatment targets. In the interim, it is critical that we recognize the vulnerability of this patient population, particularly women with severe manifestations of placental vascular disease. Women with severe early-onset disease and fetal growth restriction require regular vascular risk assessments, and placental disease should be ascertained in our patients' histories to assist with risk stratification. Cardiovascular risk factors should be aggressively targeted with lifestyle modifications and, if necessary, pharmacologic therapy.

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