Seminars in Perinatology 38 (2014) 146–150

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Long-term maternal morbidity and mortality associated with ischemic placental disease

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ARTICLE INFO

Keywords:
Ischemic placental disease
Long term maternal morbidity
Preeclampsia
Placental abruption
Fetal growth restriction

ABSTRACT

Ischemic placental disease can have long-term maternal health implications. In this article, we discuss the three conditions of ischemic placental disease (preeclampsia, fetal growth restriction, and abruption placenta) and its associated long-term maternal morbidity. Retrospective observational studies comparing pregnancies complicated by ischemic placental disease to uncomplicated pregnancies suggest an increased long-term risk of hypertension, cardiovascular death, metabolic syndrome, and cerebrovascular disease. This association is much stronger in women who had an indicated-preterm delivery due to ischemic placental disease. It is important to adequately counsel women who are diagnosed with these conditions about their future health risks. Increased awareness of the potential health risks and multidisciplinary collaboration remains paramount to instituting the appropriate screening and preventative strategies (i.e., behavior modification) for affected women.

Introduction

Ischemic placental disease is a term used to cluster together the constellation of clinical manifestations associated with uteroplacental ischemia (preeclampsia, fetal growth restriction, and placental abruption) frequently leading to preterm birth.[1] By studying these clinical manifestations as one entity, more precise information can be gleaned from epidemiologic, predictive, and treatment perspectives. It has also provided useful information regarding recurrence risks in future pregnancies.[2] As pregnancy outcomes are increasingly being recognized as predictors of long-term health, identifying ischemic placental disease as a pregnancy outcome will likely also serve as an important risk assessment for individualized health maintenance.

While one pregnancy often predicts the success/potential problems in future pregnancies, obstetrical history also has the ability to predict future health outcomes. Pregnancy can be viewed as a stress-test, providing a window into the development of later health complications based on how the stressful anatomic and physiologic changes of pregnancy are handled. This was earliest identified in relation to a woman's risk of developing type 2 diabetes. The relationship between gestational diabetes and future type 2 diabetes has been well established,[3] such that routine screening in pregnancy was developed for just this purpose. Metabolic responses tend to repeat themselves across pregnancies and have been used to identify women with lower thresholds for carbohydrate intolerance with advancing age.

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http://dx.doi.org/10.1053/j.semperi.2014.03.003
0146-0005/

Vasoactive responsiveness, angiogenesis, coagulation thresholds, and endothelial function are related to cardiovascular morbidity in the non-pregnant population. Dysregulation of these homeostatic regulatory systems, in addition to inflammation and autoimmune tendencies, may become unmasked during pregnancy and are the hallmarks of ischemic placental disease. After the stress of pregnancy is removed, age-related factors are added and long-term morbidity surfaces. This article reviews the various types and degrees of maternal health risks that have been identified among women experiencing a pregnancy complicated by ischemic placental disease.

Preeclampsia

Preeclampsia is a well-known obstetrical complication with its origin within the uteroplacental unit. Preeclampsia complicates 3–5% of all pregnancies, with increased risks noted among women who are obese, are at extremes of age, have pre-gestational diabetes, and/or have increased baseline blood pressures. The maternal and fetal morbidity and mortality associated with preeclampsia is well-accepted. However, there is less awareness among obstetricians and non-obstetrician providers of the long-term health risks associated with preeclampsia, and the appropriate follow-up care and counseling of women who have had affected pregnancies.[4,5]

Preeclampsia has been studied with regard to long-term cardiovascular disease, stroke, mortality, insulin resistance, and even psychosocial outcomes. Since 1961, it has been known that women with preeclampsia have an increased risk of long-term hypertension.[6] In recent studies, the risk of long-term hypertension after preeclampsia is approximately three-fold that of women with normal pregnancies.[7–11] This risk appears to be further increased in the setting of recurrent preeclampsia.[10] This same study found a 3.7-fold [95% confidence interval (CI): 3.0–4.5] increased risk of type 2 diabetes mellitus in women with severe preeclampsia. Other cardiovascular risk factors have also been found to be increased in women with a history of preeclampsia. Forest et al.[12] studied 168 women with hypertensive disorders of pregnancy and 168 women with normal pregnancies, 7.8 years after pregnancy to determine their cardiovascular risk profile. They found that women with hypertensive disorders of pregnancy had higher BMIs, systolic and diastolic blood pressures, fasting blood glucose levels, and insulin levels, and they had lower high-density-lipoprotein cholesterol levels than women without hypertensive disorders. After adjusting for confounders, the high–blood pressure group was 3.6 times (95% CI: 1.4–9.0) more likely to have metabolic syndrome, which is a well-known risk factor for cardiovascular disease. Fraser et al.[13] had a similar finding in that hypertensive disorders of pregnancy were associated with an increased calculated 10-year cardiovascular disease risk based on the Framingham prediction score (OR = 1.31, 95% CI: 1.11–1.53). This included an increased BMI, blood pressure, waist circumference lipids, and insulin.

Not all markers of future cardiovascular disease have been demonstrated in women with a history of preeclampsia. Neither McDonald et al.[11] nor Sandvik et al.[14] were able to find differences in subclinical atherosclerosis, as measured by carotid artery intima thickness between women with and without remote histories of preeclampsia. They did, however, have a higher rate of hypertension (32% vs. 10%, $p < 0.01$), and increased waist (88.6 vs. 84.7 cm, $p = 0.008$) and hip (108.4 vs. 104.2 cm, $p = 0.001$) circumferences.[11] Sandvik et al.[14] also measured flow-mediated dilation of the brachial artery in women 10 years after pregnancies with and without hypertensive disorders and found no difference between the two groups. Though they did find a difference in other markers of endothelial dysfunction between the two groups in this study. They found that women with preeclampsia had higher levels of urate and soluble fms-like tyrosine kinase and lower levels of high-density-lipoprotein cholesterol. Östlund et al.[15] also compared markers of endothelial dysfunction between women who had normal and preeclamptic pregnancies. They found that while women with preeclamptic pregnancies had markers of endothelial dysfunction 1 year after the index pregnancy, this was normalized by 11 years post pregnancy.

Although endothelial dysfunction appears to normalize after preeclamptic pregnancies, these women remain at risk for adverse cardiovascular outcomes, including dysrythmias and heart failure, compared with non-preeclamptic women.[16] They also have a 2.1–2.7-fold increased risk of cardiovascular death, which increases to 8.12–9.54-fold if the preeclampsia resulted in a preterm delivery at less than 34 weeks.[17–19] The increased cardiovascular risk profile of women with preeclamptic pregnancies does not appear to be affected by whether they receive magnesium sulfate, or if they undergo labor induction rather than expectant management.[20,21]

Epidemiologic data suggests that in addition to an increased risk of cardiovascular disease, cerebrovascular disease risk is also increased in women with a history of preeclampsia, as these women have been found to have an increased risk of stroke.[7,22] Aukes et al.[23] postulate that this risk may be associated with an increase in the amount and severity of white matter lesions observed, although a cause–effect relationship has not been established.

In addition to the physical health consequences of preeclampsia, studies have also reported increased incidences of anxiety, depression, and posttraumatic stress symptoms.[24,25]

Fetal growth restriction

Much of the work on fetal growth restriction and future cardiovascular disease has focused on the risk to the offspring, as demonstrated in both epidemiologic studies and animal models. The concept of fetal programming and the impact of the intrauterine environment on offspring have drawn significant interest. Much less is understood regarding the long-term health impact on the mother who delivers a growth-restricted infant due to placental ischemia. Although the etiologies of fetal growth restriction vary widely, a considerable percentage is the result of underperfusion of the uteroplacental unit and may or may not be associated with maternal preeclampsia or abruption. The underlying placental dysfunction common to this and other manifestations of ischemic placental disease suggests that there would