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First trimester prediction of ischemic placental disease

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ABSTRACT

Ischemic placental disease is characterized by one or more of the clinical manifestations of preeclampsia, fetal growth restriction, and/or placental abruption, resulting in indicated preterm delivery. Since over half of the indicated preterm deliveries are due to ischemic placental disease, accurate early prediction of the disease is of paramount importance in developing prevention strategies. This review article focuses on studies that have used the first trimester aneuploidy screening timing window to predict those patients who later develop ischemic placental disease. Emphasis was given to studies originating from the Fetal Medicine Foundation because of their uniformity in definitions and expertise of the personnel who performed the ultrasound screening exams.

Introduction

Preterm delivery continues to be a major contributor to long-term morbidity and mortality.[1] The United States data indicate that approximately 60% of preterm deliveries result from spontaneous preterm delivery (spontaneous onset of labor or pre-labor rupture of membranes) and 40% from indicated preterm deliveries.[2] The most frequent conditions leading to indicated preterm delivery are remarkably similar between singleton and twin pregnancies and include preeclampsia, fetal growth restriction, and placental abruption[3,4] (Table 1). More than half of indicated preterm deliveries are linked to these three conditions.[5]

Definition and pathophysiology of ischemic placental disease

We have previously hypothesized that preterm preeclampsia, fetal growth restriction, and placental abruption are different clinical manifestations of a common pathophysiology characterized by abnormal trophoblast invasion, and we have used the term "ischemic placental disease."[5] Our hypothesis was based on several reasons. First, there is frequent coexistence of the above three conditions, especially in pregnancies that necessitate early preterm delivery (less than 34 weeks). In a study of 2434 women diagnosed with preeclampsia, the prevalence of fetal growth restriction was 18.2% in early preeclampsia as compared to 8.6% in the general hospital population and 5.6% (reduced) in late-onset preeclampsia.[6] The prevalence of placental abruption (8.3%) and perinatal mortality rate (28.7%) were significantly higher in early-onset preeclampsia and fetal growth restriction. Second, there are remarkable similarities in the clinical characteristics, risk factors, placental histology, Doppler velocimetry, and angiogenic and anti-angiogenic placental factors. In fact, the similarities in these characteristics appear more homogeneous among preterm deliveries, indicating that endothelial cell dysfunction is involved in the

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Table 1 – Conditions leading to indicated preterm delivery in singleton and twin gestations.

Indications for delivery	Singleton pregnancies[3] (%)	Twin pregnancies[4] (%)
Preeclampsia	43	44
Growth restriction/ fetal distress	37	33
Placental abruption	7	9
Fetal death	7	7
Other	6	7

pathogenesis of all these conditions.[7] Third, there is an increased crossover recurrence of ischemic placental disease, with those who develop preeclampsia being at a high risk for developing any of the other two conditions (fetal growth restriction or placental abruption) and vice versa.[8] Fourth, mothers whose pregnancies are complicated by either preterm preeclampsia or fetal growth restriction are at a particularly high risk for developing cardiovascular disease later in life.[7] Fifth, there are remarkable similarities in the placental bed biopsy findings in all these three conditions. In early preeclampsia, there is total absence of myometrial spiral artery remodeling; in preeclampsia with fetal growth restriction and also in abruptio placenta there is also total absence of myometrial spiral artery remodeling and "obstructive" lesions.[9]

In normal pregnancies, the trophoblastic invasion of the uterine spiral arteries begins at approximately 8–10 weeks and is almost completed by 16–18 weeks, although the second phase can last up to 24 weeks.[10] In ischemic placental disease there is inadequate and incomplete trophoblast invasion of maternal spiral arteries, starting as early as 8–10 weeks' gestation, leading to preterm preeclampsia, fetal growth restriction, and/or placental abruption. The degree and timing of the abnormal trophoblast invasion will most likely define the particular clinical manifestations, which could be either preterm preeclampsia alone or preterm preeclampsia associated with fetal growth restriction with or without placental abruption. This pathophysiology should be distinguished from term preeclampsia that is usually associated with normal fetal growth, normal blood flow, and frequently accompanied by large placental mass.

In ischemic placental disease, the abnormal trophoblast invasion will lead to reduced uteroplacental blood flow (which can be detected by Doppler ultrasound) and uteroplacental ischemia, resulting in over- or under-production of various angiogenic and anti-angiogenic factors, which could be detected by maternal serum screening. Attempts at predicting and preventing ischemic placental disease in the general population have been unsuccessful mainly because the timing of these attempts was too late—in the second trimester—long after the completion of the process of abnormal trophoblast invasion.

Prevention of ischemic placental disease

Given the early invasion of the placental trophoblast, the ideal timing for prediction and start of preventive therapy should be in the first trimester of pregnancy. For nulliparous women or women at high risk for preeclampsia, based on history and/or ultrasound findings, recent meta-analyses showed that low-dose aspirin (50–150 mg/day) starting at ≤16 weeks is associated with approximately 60% reduction in perinatal deaths, 50% reduction in preeclampsia, 80–90% reduction in early severe preeclampsia (<34 weeks), 50–55% reduction in fetal growth restriction, and 65–80% reduction in preterm delivery.[11,12] The mechanism of action of low-dose aspirin is not entirely understood, but it is possible that it may promote trophoblast invasion of uterine spiral arteries, thus reversing the incomplete invasion.[11]

First trimester prediction of ischemic placental disease

Since the results of the above two meta-analyses, the tremendous amount of research and the extremely high number of publications regarding prediction of preeclampsia and/or fetal growth restriction in the first trimester of pregnancy is well justified. Ideally, accurate prediction of ischemic placental disease by screening the entire population (low- and high-risk pregnancies) could lead to dramatic decreases in severe early preeclampsia, fetal growth restriction, prematurity, and perinatal death rate by using low-dose aspiring for those identified as "high risk." However, the road to "accurate" prediction has been long and difficult given the low sensitivities and low positive predictive values of the individual clinical factors (derived from maternal history/maternal characteristics); Doppler studies, the most commonly being used uterine artery pulsatility index (UtA PI); and the individual maternal serum (placental/biochemical) factors.

Most of the research in the prediction of ischemic placental disease in the first trimester of pregnancy originates from the Fetal Medicine Foundation. Kypros Nicolaides' group capitalized on the 11–13 weeks' gestation window that they use for aneuploidy screening by developing the philosophy that the timing and prediction models should follow the same statistical approach as in the screening for trisomy 21. This statistical approach uses a combination of clinical factors (based on maternal history/characteristics), UtA PI, and maternal biophysical and biochemical markers to derive patient-specific risks for ischemic placental disease. Table 2 depicts the most pertinent 32 studies, involving the use of ultrasound (mainly UtA PI) with or without biophysical or biochemical serum markers, for first trimester prediction of ischemic placental disease. The table shows the evolution of the research findings by using different biophysical and biomedical markers alone and in combination, and it summarizes the findings of each pertinent study with special emphasis in the detection of severe early preeclampsia and SGA necessitating preterm delivery at less than 34 weeks. We included mainly studies produced from the Fetal Medicine Foundation because of the uniformity in training and certification of the personnel who perform the first trimester screening exam. These studies showed that the first trimester predictions of preeclampsia and SGA are much stronger for the pregnancies necessitating preterm delivery as compared to near-term or term gestations. The predictions for late