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Epidemiology of ischemic placental disease: A focus on preterm gestations

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ABSTRACT

Preeclampsia, placental abruption, and intrauterine growth restriction (IUGR) have collectively been termed ischemic placental disease (IPD) due to a suspected common biological pathway involving poor placentation in early pregnancy and subsequent placental insufficiency. Despite decades of research, the etiologies of these conditions remain largely unknown and preventive and therapeutic strategies are lacking. It has been suggested that the underpinnings of IPD lie primarily in preterm gestations and that classification of these conditions based on the gestational age at onset will facilitate etiologic research. The purpose of this review is to describe our current knowledge regarding the risk factors, co-occurrence, and recurrence of the conditions of IPD with a specific focus on the preterm gestational window.

Introduction

Preeclampsia, placental abruption, and intrauterine growth restriction (IUGR) have collectively been termed ischemic placental disease (IPD) because they are frequently characterized by uteroplacental underperfusion, chronic hypoxia, and placental ischemia, which are results of poor trophoblast invasion and incomplete remodeling of the spiral arteries during placentation.[1,2] Thus, a suspected common biological pathway involving poor placentation in early pregnancy and subsequent placental insufficiency has been implicated in their development, yet their etiologies remain largely unknown and preventive and therapeutic strategies are lacking.[1] These 3 conditions combined contribute to more than half of all medically indicated deliveries before 35 weeks in the United States and are associated with disproportionately high rates of perinatal morbidity and mortality.[3–6]

Although the cause of these 3 conditions remains elusive, several pathologic processes have been proposed including endothelial dysfunction, abnormal placentation, and infection and inflammation.[7] While evidence is available to support varying pathologic processes in the development of conditions of IPD, recent evidence suggests that homogeneity of the risk profiles can be observed when these conditions occur in preterm gestation.[8] The purpose of this review is to describe the risk factors, co-occurrence, and recurrence of the conditions of IPD with a specific focus on the preterm gestational window.

Preeclampsia

Preeclampsia, typically defined as the de novo onset of hypertension and proteinuria after the 20th week in gestation, complicates approximately 2–8% of pregnancies.[9–11] Rates of preeclampsia have declined in several European nations and Australia within the last decade,[12,13] while increases in preeclampsia, specifically severe preeclampsia,

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have been observed in the United States.[10,14] Despite the increasing prevalence of several risk factors for preeclampsia worldwide, the observed decline in the incidence of preeclampsia in some countries is speculated to be a result of increasing rates of early elective delivery among high-risk women.[13] Risk factors for preeclampsia include advanced maternal age, obesity, and chronic health conditions that affect vascular function, such as pre-existing diabetes, chronic hypertension, kidney disease, and antiphospholipid syndrome.[15] Nulliparity is one of the most consistently identified risk factors for preeclampsia. Data from the Swedish Medical Birth Register demonstrated a risk of preeclampsia of 4.1% in a first pregnancy that decreased to 1% in the second pregnancy for women without preeclampsia in their first pregnancy.[16] However, multiparous women with a previous pregnancy affected by preeclampsia have the greatest risk.[1] Partner change between pregnancies[17] and extended interpregnancy intervals[9,18] are also associated with an increased risk of preeclampsia.

Preeclampsia can be classified as early onset, preferably defined as preeclampsia occurring before 34 weeks' gestation,[19] but clinical definitions of early onset are varied and epidemiologic studies have not been consistent, with classifications ranging from <32 to <37 weeks. Early-onset preeclampsia is a more severe condition and is thought to originate from poor placentation as evidenced by the increased likelihood of IUGR in these pregnancies. In the case of late-onset preeclampsia, fetal growth remains largely unaffected indicating less placental involvement in the pathogenesis of this condition.[20] Compared to women without preeclampsia, the risk of a fetus being small for gestational age among women with early-onset preeclampsia is increased 7-fold, whereas the corresponding risk is a 3-fold increase for late-onset preeclampsia.[21]

Differences in risk factors for early- and late-onset preeclampsia have also been noted.[21] Women with chronic hypertension have a higher risk of early- but not late-onset preeclampsia.[21] Overweight and obese women, as measured by BMI, have greater risk of late-onset preeclampsia than early-onset preeclampsia.[22] Nulliparity and diabetes mellitus were also more strongly associated with late-onset disease, while young maternal age was associated with a decreased risk of early-onset preeclampsia, but not late onset.[21] The differential risk patterns according to gestational age at onset support the notion that these conditions represent distinct clinical entities. Further, early-onset preeclampsia is more consistent with the defining features of IPD than late-onset preeclampsia.

Placental abruption

Placental abruption, defined as complete or partial separation of the placenta prior to delivery, is the least common of the 3 IPD conditions with an estimated prevalence of 1% in the United States.[23] The prevalence is lower in Nordic countries, approximately 0.4–0.5% in Sweden[24] and Finland.[25] An increasing incidence of placental abruption has been reported in the United States,[26] while decreasing rates have been observed in Finland.[25] While several risk factors for placental abruption are generally increasing in prevalence, reported declines may be due to improved monitoring of high-risk pregnancies and early delivery of these pregnancies prior to the occurrence of an abruption. Risk factors for placental abruption include advanced maternal age, multiparity, cigarette smoking, and drug use during pregnancy. Chronic hypertension and pre-gestational diabetes are also risk factors.[27,28] The greatest risk factor for abruption is a prior placental abruption, with estimates ranging from 3- to 12-fold increased risk of a subsequent abruption.[1,24]

Preterm placental abruption (<37 weeks) and term placental abruption (≥ 37 weeks) are suspected to have varied biological mechanisms, but studies distinguishing between preterm and term abruption are limited. Preterm placental abruption is estimated to be 9 times more common than term abruptions, with a rate of 2.8% among preterm births and 0.3% among term births in the United States.[29] Risk factors and conditions associated with preterm abruption differ from those associated with term abruption, implicating that these 2 diagnoses are distinctive.[29] One study that distinguished between timing of abruption observed lower mean birth weights and placental weights in preterm abruption births, but not term abruption births, indicating that preterm abruption may be more consistent with placental ischemia.[30] Other studies have assessed factors associated specifically with preterm abruption among preterm births[31] or term placental abruption among term births.[32] Smoking in pregnancy, hypertension, and intravenous drug use were associated with abruption among preterm births, while advanced maternal age was associated with abruption among term births. Due to the limitations of including only preterm or term births in each of these studies, a comparison of risk factors between preterm and term abruption cannot be performed.

Intrauterine growth restriction

Intrauterine or fetal growth restriction is described as the failure of a fetus to reach its predetermined growth potential. IUGR is a difficult antenatal diagnosis requiring a detailed assessment of maternal risk factors, including reproductive history and chronic conditions, pregnancy risk factors, and serial ultrasounds among women identified as at risk.[33] Due to the amount of information required to confer a diagnosis of IUGR, specifically serial ultrasounds and Doppler studies, epidemiologic studies frequently use small for gestational age (SGA) as a proxy for IUGR. It should be noted that a large proportion of SGA infants are not actually growth restricted but are either constitutionally small or small due to physiologic reasons, such as congenital malformations. IUGR affects an estimated 3–5% of pregnancies. Placental insufficiency, as measured by structural abnormalities and histologic findings, is the most frequent cause of IUGR, but fetal factors, including chromosomal abnormalities and congenital infections, and maternal risk factors also contribute to IUGR.[34]

Risk factors for IUGR include smoking during pregnancy, low pre-pregnancy weight , and low weight gain.[35] Diabetes mellitus and hypertension are also associated with IUGR. One of the strongest risk factors for IUGR in a current pregnancy is a previous IUGR-affected pregnancy.[36]