Pathophysiology of placental-derived fetal growth restriction

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Placental-related fetal growth restriction arises primarily due to deficient remodeling of the uterine spiral arteries supplying the placenta during early pregnancy. The resultant malperfusion induces cell stress within the placental tissues, leading to selective suppression of protein synthesis and reduced cell proliferation. These effects are compounded in more severe cases by increased infarction and fibrin deposition. Consequently, there is a reduction in villous volume and surface area for maternal-fetal exchange. Extensive dysregulation of imprinted and nonimprinted gene expression occurs, affecting placental transport, endocrine, metabolic, and immune functions. Secondary changes involving dedifferentiation of smooth muscle cells surrounding the fetal arteries within placental stem villi correlate with absent or reversed end-diastolic umbilical artery blood flow, and with a reduction in birthweight. Many of the morphological changes, principally the intraplacental vascular lesions, can be imaged using ultrasound or magnetic resonance imaging scanning, enabling their development and progression to be followed in vivo. The changes are more severe in cases of growth restriction associated with preeclampsia compared to those with growth restriction alone, consistent with the greater degree of maternal vasculopathy reported in the former and more extensive macroscopic placental damage including infarcts, extensive fibrin deposition and microscopic villous developmental defects, atherosis of the spiral arteries, and noninfectious villitis. The higher level of stress may activate proinflammatory and apoptotic pathways within the syncytiotrophoblast, releasing factors that cause the maternal endothelial cell activation that distinguishes between the 2 conditions. Congenital anomalies of the umbilical cord and placental shape are the only placental-related conditions that are not associated with maldevelopment of the uteroplacental circulation, and their impact on fetal growth is limited.

Key words: AKT/mTOR, apoptosis, atherosis, chorion laeve, electron transport chain, extravillous trophoblast, failure of physiologic transformation, fetal growth restriction, fetoplacental weight ratio, hemochorial placentation, interstitial trophoblast, intervillous space, intraplacental oxygen concentration, mitochondria, oxidative stress, perivillous fibrin deposition, placenta, placental infarct, placental inflammation, placental location, reactive oxygen species, spiral arteries, ultrasound imaging, unfolded protein response, villi regression, villous hypoplasia

Introduction

The kinetics of placental and fetal growth are closely interrelated, and are important features predicting postnatal health and in particular cardiovascular adaptations in childhood.[1,2] Fetal growth is dependent on nutrient availability, which in turn is related to the maternal diet, uteroplacental blood supply, placental villous development, and the capacity of the villous trophoblast and fetoplacental circulation to transport these nutrients. At birth, the fetoplacental weight ratio gives a retrospective indication of the efficiency of the placenta to support growth of the fetus, and estimates the potential risks for chronic diseases in later life through developmental programming.[2,3]

Fetal growth restriction (FGR) is defined as the failure of the fetus to achieve its genetically determined growth potential.[4] FGR can have many causes, but the majority of cases that are not associated with fetal congenital malformations, fetal genetic anomalies, or infectious etiology are thought to arise from compromise of the uterine circulation to the placenta. Sufficient dilatation of the uteroplacental circulation together with rapid villous angiogenesis are the key factors necessary for adequate placental development and function, and subsequent fetal growth.

The etiopathology of FGR due to abnormal development of the uteroplacental circulation and its impact on placental development and structure has been studied for >5 decades.[5] Ultrasound imaging, and in particular color Doppler imaging, has allowed the study of both the umbilicoplacental and uteroplacental circulations from the first trimester of gestation onward.[6,7] These techniques have been used extensively in the screening of placental-related complications of pregnancy, such as preeclampsia,[8,9] and the management of a fetus presenting with primary or secondary FGR.[10] More recently, 3-dimensional Doppler imaging[11,12] and magnetic resonance imaging (MRI)[13] have been used to study the development of the placental and fetal circulations, but their use in clinical practice remains limited.

Placental-related complications of pregnancy that lead to FGR have their

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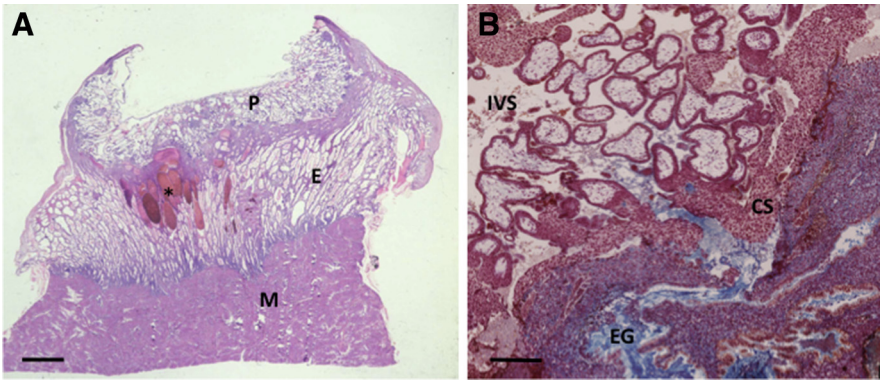
FIGURE 1
Histotrophic nutrition of the placenta during the first trimester



Photomicrographs of archival placenta (P) in situ specimen (H710) at 6 weeks' gestational age demonstrating histotrophic nutrition. **A**, Gestational sac with developing P is implanted in superficial endometrium (E), and was opened during processing to remove embryo. Glands in E beneath sac are highly active, although hemorrhage occurred in some (*). Scale bar = 2 mm. **B**, Higher power view of interface between P and E showing opening of E gland (EG) into intervillous space (IVS) through cytotrophoblastic shell (CS) and developing basal plate. Scale bar = 250 μm. Modified.[16,177]

M, myometrium.

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pathophysiological roots in the early stages of placentation and can manifest themselves from the end of the first trimester of pregnancy when the definitive placenta is forming.[14,15] Considerable remodeling of the placenta takes place toward the end of the first trimester/start of the second trimester, associated with onset of the maternal arterial circulation when the placenta becomes fully hemochorial. Events at this time potentially impact the final size of the placenta, and hence it functional capacity. This concept is supported by findings in utero showing that pregnancies complicated with FGR, with or without accompanying preeclampsia later in pregnancy, have a smaller placenta volume and higher uterine resistance to blood flow compared to healthy controls from the beginning of the second trimester.[9]

The relationships between abnormal placental development and FGR are complex. Isolating the placental causes of FGR can be difficult as many clinical studies are small, retrospective, and often multivariate with confounding factors such as maternal smoking and ethnicity. Also, many potential stressors converge on the same intracellular pathways, and separating the influence of, for example, glucose as compared to oxygen deprivation during periods of ischemia is impossible.

To provide a coherent account of how the FGR phenotype may arise we first consider the development of the normal placenta before discussing the molecular and clinical pathologies.

Early development of the placenta

Initial development of the placenta takes place within the superficial layer of the endometrium, and by the end of the third week postconception villi have formed over the entire chorionic sac. This precocious growth is supported and stimulated by secretions from the underlying endometrial glands (Figure 1),[16,17] so-called histotrophic nutrition. The carbohydrate- and lipid-rich secretions are delivered through openings in the developing basal plate into the intervillous space, from where they are taken up by the syncytiotrophoblast. As well as providing nutrients, the secretions contain numerous growth factors that stimulate placental cell proliferation in vitro, and most likely play an important role in regulating development and differentiation in vivo.[18-20] The absence of significant maternal blood flow at this stage means that initial development takes place in a low oxygen concentration, which is physiological and should not be considered hypoxic.[21] This environment is thought to protect the embryo from damaging reactive oxygen species (ROS) during the period of organogenesis, but may also serve to maintain stem cell potential.[22] Once the main organs have differentiated there is a need for a greater supply of oxygen to support faster fetal growth,[23] and hence there must be a switch from histotrophic nutrition to hemotrophic supply from the maternal circulation.

Development of the uteroplacental circulation

The human hemochorial form of placentation poses major hemodynamic challenges. In particular, a high volume of maternal arterial blood flow has to be delivered to the placenta at a sufficiently low pressure and velocity to prevent mechanical damage to the delicate villous trees.[24] In normal pregnancies, the arcuate and radial arterial components of the uterine vasculature dilate under the combined effects of estrogen, progesterone, human chorionic gonadotropin, and other hormones and factors secreted by the placenta. The dilation accommodates the increased uterine flow of pregnancy, and is so marked that by around 20 weeks of gestation the diameter of the arcuate arteries is equal to that of the uterine artery.[25] The more distal elements of the uteroplacental vasculature undergo additional extensive remodeling under the influence of extravillous trophoblast cells that migrate out from the placenta during early pregnancy. This remodeling involves the loss of smooth muscle cells and elastin from the arterial walls, and their replacement by fibrinoid material.[26] As a result, these segments of the uteroplacental vasculature become inert flaccid conduits, incapable of vasoconstriction. The