CHAPTER 7

Potential Role of Glucocorticoids in the Pathophysiology of Intrauterine Growth Restriction (IUGR)

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Abstract

Although the etiology of intrauterine growth restriction (IUGR) and preeclampsia (PE) remains unclear, most investigators attribute the initial “insult” to poor utero-placental perfusion due to defective trophoblast invasion that ultimately compromises fetal well-being. The resultant hypoxia curtails the remodeling of uterine vessels by invasive cytotrophoblasts in the second trimester. Our results suggest that mediators of fetal stress [i.e., glucocorticoids (GC)] may in fact alter placental gene expression and contribute to the destruction of the placental villous network in pregnancies with IUGR/PE. We will present a molecular model through which GC, induced in response to fetal stress, promotes the placental villous damage observed in pregnancies associated with IUGR/PE. This model incorporates the roles of trophoblast plasminogen activator inhibitor (PAI)-1, mesenchymal extracellular matrix (ECM) proteins, and their regulation by transforming growth factor (TGF)-β. We will employ the term “lUGR/PE” to describe those pregnancies with severely growth-restricted fetuses may also complicated by maternal PE. These conditions frequently coexist, and a review of the literature suggests that this placental pathology may be associated with both IUGR and PE. Furthermore, considerable attention has been given to the role of exogenously administered and stress-induced endogenous increases in fetal GC and the development of IUGR. There is mounting evidence that aberrant elevations in GC during fetal life and/or IUGR may result in fetal programming of chronic diseases of adulthood such as diabetes, coronary artery disease, and hypertension.

Excess Placental Fibrin and ECM Proteins Are Noted in Pregnancies with IUGR/PE

The most severe cases of IUGR/PE are associated with 40 to 50 percent fetal mortality and are usually characterized by absent or reversed end diastolic flow (AEDF or REDF) in the umbilical artery. Placentas delivered from pregnancies with AEDF show a higher frequency of maldeveloped, elongated, poorly branched, and poorly vascularized terminal villi, the principal sites of nutrient and oxygen exchange between mother and fetus. Although the precise etiology of these changes in placental structure is not known, it is generally thought to result from defective cytotrophoblast invasion in the first two trimesters of pregnancy. Histological studies of IUGR/PE placentas have revealed two specific biochemical changes relative to controls matched for gestational age; excessive perivillous (i.e., in the intervillous space) deposition of fibrin and up-regulation of ECM proteins in the villous core.

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Figure 1. Placental pathophysiology in IUGR. Based on several studies, we and others suggest that aberrant deposition of intervillous fibrin and intravillous ECM proteins lead to collapse of the villous network (infarction) in pregnancies associated with severe IUGR. This results in a reduction in the transfer of oxygen and nutrients from mother to fetus.

analyses have demonstrated thickened basal lamina and increased expression of collagen III and IV and laminin in the core of the placental villus in pregnancies with IUGR/PE. In this same study, electronmicroscopy identified placental mesenchymal cells (PMCs) as the likely source of enhanced ECM protein expression noted in IUGR/PE placentas. Furthermore, in pregnancies with IUGR/PE, excessive perivillous deposition of fibrin and intravillous ECM proteins was associated with extensive placental villous damage (increased prevalence of white infarcts or collapsed villi, necrosis, and fibrosis) and impairment of nutrient transport. Thus, it is likely that hyper-accumulation of perivillous fibrin and placental ECM proteins in pregnancies associated with IUGR/PE disrupts placental architecture, collapses the villous network, and irreversibly restricts the flow of nutrients between mother and fetus (Fig. 1). We do not propose that excessive deposition of fibrin and ECM proteins cause IUGR, but rather that they play a critical role in the pathophysiology of these pregnancies. In addition, we acknowledge that there are several other potential cellular mechanisms of placental damage in pregnancies with IUGR and PE including apoptosis, hypoxia and reperfusion injury, all of which may be affected by GC. However, for the purpose of this report we are limiting our discussion to a potential unifying mechanism underlying excessive placental fibrin and ECM protein deposition in these pregnancies.

Plasminogen Activator Inhibitor (PAI-1): Role in Fibrin Deposition in Pregnancy

PAI-1 is a 52 kD protein that is a member of a serpin (serine protease inhibitor) family of protease inhibitors that also includes PAI-2 and PAI-3. PAI-1 is the primary inhibitor of fibrinolysis based on its high affinity suppression (Kᵢ = 1 nM) of tissue type plasminogen activator (tPA). PAI-1 forms a 1:1 molecular complex with tPA and inhibits tPA-mediated conversion of plasminogen to plasmin, the major fibrinolytic factor. PAI-1 was originally described as an endothelial cell protein, but later reports revealed PAI-1 to be synthesized by many cell types, including those found at the uterine-placental interface, e.g., trophoblasts and decidual cells. Interaction with the ECM protein vitronectin stabilizes PAI-1 and may localize it to areas of thrombosis. Excessive production of PAI-1 would be expected to compromise fibrin clearance when the clotting cascade is activated. Pregnancy is considered to be a thrombophilic state based on the elevation of several plasma coagulation factors (e.g., factor VII, VIII, X and fibrinogen) in maternal sera across gestation.