Diabetes Mellitus and Preeclampsia

Mohammad Nasir Uddin1,2, Madhava R. Beeram2 and Thomas J. Kuehl1,2,3

1 Departments of Obstetrics & Gynecology, Texas A&M Health Science Center College of Medicine/ Scott & White Healthcare, USA
2 Department of Pediatrics, Texas A&M Health Science Center College of Medicine/ Scott & White Healthcare, USA
3 Department of Molecular & Cellular Medicine, Texas A&M Health Science Center College of Medicine/ Scott & White Healthcare, USA

Abstract

Preeclampsia (preE) is a pregnancy disorder characterized by the de novo development of hypertension and proteinuria after 20 weeks of gestation and is the leading cause of maternal and fetal morbidity and mortality. The specific etiologies of this syndrome remain unknown. However, it seems clear that preE is not a single disorder, but a syndrome with multiple pathophysiologic triggers and mechanisms. Approximately 20% of the diabetic women who become pregnant develop preE. The mechanisms contributing to this effect is not well characterized. There is considerable evidence to suggest that dysfunction of cytotrophoblast cells, which are critical for formation of the fetal-maternal interface, may play a central role in the pathogenesis of preE. Excessive circulating glucose, caused by diabetes or other conditions, is one well-characterized precursor of preE. This review evaluates the potential linkage between the risk of developing preE and the presence of diabetes early in pregnancy. The concept is that high levels of glucose may stimulate one or more mechanisms of vascular remodeling during implantation and placental development. Elevated glucose levels in pregnancy may impair a cascade of vascular development that will predispose to development of placental vascular compromise. Cytotrophoblasts organize placental remodeling during pregnancy, and excess glucose in diabetic pregnancy may triggers intracellular changes in several stress signaling pathways resulting in cytotrophoblast cell dysfunction and abnormal placentation, thus development of preE.

INTRODUCTION

Preeclampsia (preE) is a pregnancy disorder characterized by hypertension and proteinuria that occurs in 3-10% of all gestations [1-3]. This syndrome is characterized by the de novo development of hypertension and proteinuria after 20 weeks of gestation and is the leading cause of maternal and fetal morbidity and mortality [1,3]. PreE is a multifaceted condition found uniquely in the pregnant patient and one that has puzzled scientists for years. It has been demonstrated that preE is not a single disorder, but a complex syndrome that is produced by various pathophysiologic triggers and mechanisms affecting 3-8% of obstetrical patients worldwide [1,4,5]. PreE, a major cause of premature delivery and maternal and fetal death [3], has a much higher incidence in women with type 1 diabetes mellitus than in the non-diabetic population (~20% vs ~5% respectively) [6]. The underlying mechanisms for the increased risk of preE in women with diabetes are unknown and predictive measures for early detection are lacking. Studies of the mechanism of the high prevalence of preE in diabetic patients could yield information related to preE and in general the mechanisms of developing vascular complications in this patient population [6]. The relationship between hyperglycemia and the development of preE has been presented in (Table 1). As shown in (Table 1), a hyperglycemic condition during early pregnancy effects placental development in the first trimester, which continues up to the term, resulting in the high risk (20%) of preE.

Hyperglycemia alters the ctb cells function

Although the genesis of preE is unknown, much research has focused on the incompleteness of placental invasion of cytotrophoblast (CTB) cells [7-9]. CTB cells demonstrate the widest array of in utero changes of all placental components, including its invasive role in implantation and adaptability for physiological change in pregnancy maintenance. CTB invasiveness is facilitated by its capacity to digest extracellular matrices through protease activation at the endometrium [10]. Serine proteases, cathepsin and metalloproteinases (MMPs),
are involved in this invasive process [11-13]. Among the MMPs, MMP-9 and MMP-2 have been shown to mediate invasion of CTB cells or a CTB cell line into Matrigel [14-15]. The invasive behavior of CTB cells is limited in time and in space and could be mediated in an autocrine way by trophoblastic factors and in a paracrine way by uterine factors. It has already been suggested that tumor necrosis factor alpha (TNF-α) could serve as an autocrine growth factor in chorioarcinoma cells and might thus facilitate proliferation of CTB cells [16]. It was shown that TNF-α induced the secretion of MMP-9 from eosinophils via p38 MAPK but not the extracellular signal-regulated kinase 1/2 (ERK1/2) pathway [17-18]. Recent studies have demonstrated that urokinase plasminogen activator (uPA) acts independently of fibrin and is involved in the regulation of cell adhesion and migration of CTB cells [19-20]. UPA mRNA and immunoreactivity have been demonstrated in CTB cells and in the first and third trimesters of human placenta and decidual cells. The expression of plasminogen activator inhibitor-1 (PAI-1) is seen in CTB cells and shown to be an integral part of establishing a stable maternal-fetal interface [21]. Excess glucose can occur during pregnancy due to pregestational or gestational diabetes mellitus (GDM). Several researchers demonstrate a direct link between preE and diabetes [22-23]. GDM alters the carbohydrate metabolism resulting in arteriosclerosis and glomerular filtration dysfunction, predisposing to preE [24]. Most recently, we have demonstrated that hyperglycemia impairs the invasive and proliferative profile of first trimester CTB cells [25].

Previous studies have demonstrated a correlation between levels of a cardiotonic steroid, marinobufagenin (MBG) and angiogenic imbalance [26]. Prior to the development of hypertension and proteinuria in a rat model of preE, an increase in MBG excretion in urine was found [27]. Normal pregnant rats injected with MBG developed hypertension and proteinuria and showed signs of intrauterine growth restriction [27]. In human studies an increased urinary excretion of MBG is seen in preE patients compared to normal pregnancy [28]. MBG inhibits CTB cell proliferation, migration and invasion, which are important for normal placental development [26,29]. MBG also induced apoptotic signaling in CTB cells and rat lung microvascular endothelial cells [30] and caused an angiogenic imbalance in a rat model of preE [31].

**Hyperglycemia activates the peroxisome proliferator-activated receptor gamma, thus impairment of placental development**

<table>
<thead>
<tr>
<th>Patient Type</th>
<th>Before Pregnancy</th>
<th>Pregnancy 0-20 Weeks Gestation</th>
<th>Pregnancy 20-40 Weeks Gestation</th>
<th>Development of preE</th>
<th>Placenta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>5% risk of preE</td>
<td>Normal</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>Normal</td>
<td>Normal</td>
<td>Elevated</td>
<td>5% risk of preE</td>
<td>Increased</td>
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<td>Elevated</td>
<td>Elevated</td>
<td>20% risk of preE</td>
<td>Decreased</td>
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<tr>
<th>Glucose Status</th>
<th>Before Pregnancy</th>
<th>Pregnancy 0-20 Weeks Gestation</th>
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Table 1: Relationship of hyperglycemia to the development of Preeclampsia.

is expressed predominantly in adipose tissue and is known to be involved in adipocyte differentiation and insulin sensitivity. Recent reports indicated that PPARγ-deficiency in mice was embryonic lethal due to abnormal placental development, suggesting that PPARγ plays an important role in normal development of the placenta [8,28]. Recent studies have shown that PPARγ is expressed in human primary trophoblast and human placental tissues, and that activation of PPARγ stimulates villous trophoblast differentiation and endocrine function [26,29]. Suwaki et al suggested that the PPARγ pathway might be involved in the impairment of placental development induced by high glucose conditions, and that VEGF might play some roles in this pathway [32]. Pretreatment with agonists of the PPARγ, rosiglitazone or pioglitazone, significantly reduced oxidative stress, COX-2 protein expression and activation of MAPKs and NF-κB in a rat model of mild forebrain ischemia/reperfusion injury [33]. An inhibitor of p38 mitogen-activated protein kinase prevents insulin-stimulated glucose transport but not glucose transporter translocation in 3T3-L1 adipocytes and L6 myotubes [34].

**Hyperglycemia induces an anti-angiogenic milieu**

High glucose induced a sustained phosphorylation of transcriptional activation of NF-κb in cardiomyocytes. Activated NF-κb signaling has an important role in high glucose-induced cardiomyocyte apoptosis and gene expression of interleukin-6 (IL-6) [35]. GDM complicates approximately 7% of all pregnancies in the United States and is on the rise; possibly due to increasing rates of obesity [36-37]. With increasing rates of obesity and GDM, one of the most successful forms of preE prevention could be through control of the patient’s glycemic state. It has been shown in a prospective study that gestational diabetes treatment can reduce preE by 30% and a recent case report has shown that dietary management in addition to insulin therapy can resolve angiogenic factor imbalance and result in a successful pregnancy outcome [38-39]. The urinary excretion of angiogenic factors over time in the rat model of preE has been studied [31]. The ratios of soluble fms-like tyrosine kinase-1 (sFLT-1) to placental growth factor (PIGF) is considered a reliable indicator of angiogenic imbalance. Comparing normal pregnant to preeclamptic rats at 3-5 days gestation demonstrated no difference. However, at both 7-10 and 17-20 days of gestation, the sFlt to PIGF ratio was significantly increased in the preE group, indicating angiogenic imbalance [31]. Most recently we have demonstrated that hyperglycemia induces an anti-angiogenic milieu in first trimester CTB cells [25]. Both progesterone and gestational diabetes increase the risk of preE [40]. The degree of severity of pregestational diabetes further increases the risk of preE. For example, a patient with diabetic nephropathy has a 2-3 times increased risk of preE development compared to a patient with uncomplicated type 1 diabetes mellitus [41-42]. Poor glucose control in the presence of hypertension can increase one’s risk for preE [5,43].

**CONCLUSION AND PERSPECTIVES**

Although we know preE is not a single disorder, however, it
has been suggested that hyperglycemia is one of the triggering factors to induce the syndrome in a segment of diabetic pregnant women. Preliminary works in our laboratory [25] and others indicates that increased concentrations of glucose have an effect similar to the development of preE. As illustrated in (Figure 1), excess glucose during pregnancy impedes the CTB cells function by induction of stress pathway signaling (P38 MAPK and PPARγ) followed by inhibition of MMP-9 leading to CTB migration and invasion complications, oxidative stress leading to placental hypoxia, and IL6 elevation leading to anti-angiogenic milieu. All of these changes appear to contribute to a final common pathway of placental dysfunction and preE.

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REFERENCES


