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Review Article

Diabetes Mellitus and Preeclampsia

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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 proteinase activation at the endometrium [10]. Serine proteases, cathepsin and metalloproteinases (MMPs),

Table 1: Relationship of hyperglycemia to the development of Preeclampsia.

Patient Type	Before Pregnancy	Pregnancy		Development of preE	Placenta
		0-20 Weeks Gestation	20-40 Weeks Gestation		
	Glucose Status				
Normal	Normal	Normal	Normal	5% risk of preE[1-5]	Normal
Gestational Diabetes	Normal	Normal	Elevated	5% risk of preE [22-24,37]	Increased
Diabetes prior to pregnancy	Elevated	Elevated	Elevated	20% risk of preE [6,23,42]	Decreased

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 choriocarcinoma 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

Peroxisome proliferator-activated receptor gamma (PPARγ) 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].

Hypergycemia 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 (PlGF) 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 PlGF 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 pregestional 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

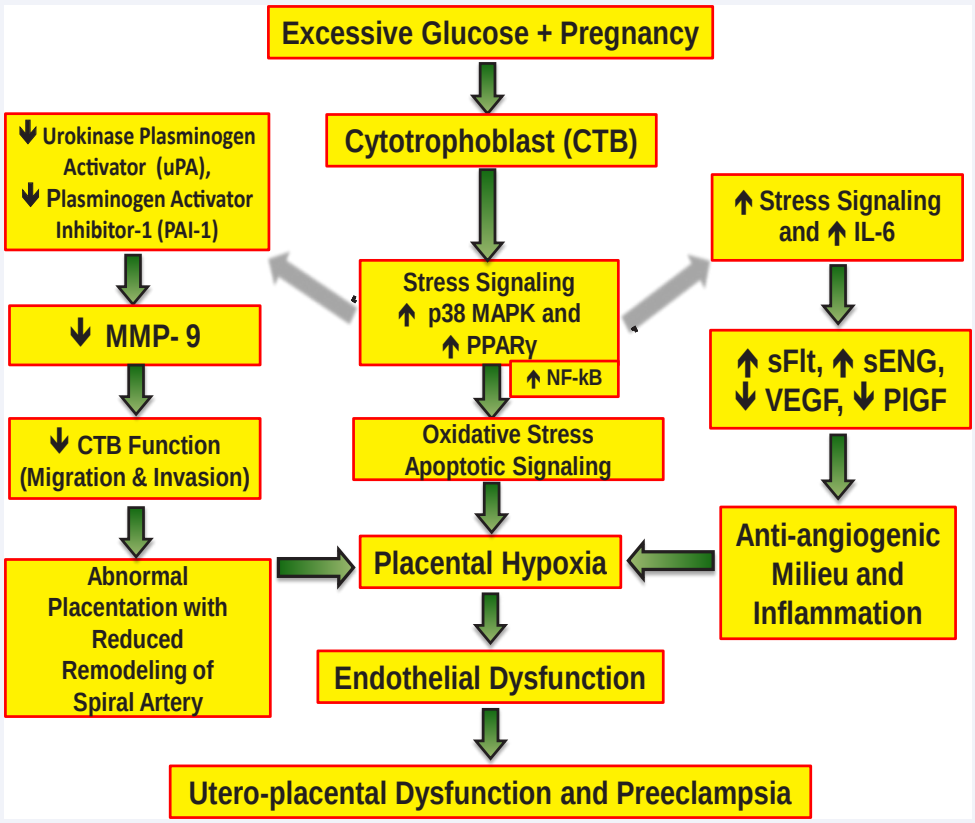

Figure 1 Possible mechanisms of hyperglycemia induced CTB cells impairment. Excess glucose hinders CTB cells by induction of stress pathway signaling (P38 MAPK and PPARγ) followed by 1) inhibition of MMP-9 leading to CTB migration and invasion problems, 2) oxidative stress leading to placental hypoxia, and 3) IL6 elevation leading to anti-angiogenic milieu. All of these changes appear to contribute to a final common pathway of placental dysfunction and preE.

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 angiogenic imbalance. All of these changes appear to contribute to a final common pathway that leads to abnormal placentation, thus the development of preE syndrome. With multiple avenues of deregulation demonstrated, and many more which were not explored, multiple treatment options can exist for those in hyperglycemic states. With preE encompassing so many mechanisms of imbalance a one size fits all treatment model seems distant and much further research is needed. Being able to understand the pathophysiologic development of CTB cell impairment in the presence of excess glucose will give us a better understanding of the relationship between diabetes mellitus and preE, helping us to provide opportunities for the development of novel treatment paradigms to prevent or treat excess glucose-induced CTB function and abnormal placentation in preE.

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REFERENCES

1. Pridjian G, Puschett JB. Preeclampsia. Part 1: clinical and pathophysiologic considerations. Obstet Gynecol Surv. 2002; 57: 598-618.
2. No authors listed] Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000; 183: S1-1S22.
3. Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. Lancet. 1993; 341: 1447-1451.
4. Anderson UD, Olsson MG, Kristensen KH, Åkerström B, Hansson SR. Review: Biochemical markers to predict preeclampsia. Placenta. 2012; 33 Suppl: S42-47.
5. Maynard SE, Karumanchi SA. Angiogenic factors and preeclampsia. Semin Nephrol. 2011; 31: 33-46.
6. Yu Y, Jenkins AJ, Nankervis AJ, Hanssen KF, Scholz H, Henriksen T, et al. Anti-angiogenic factors and pre-eclampsia in type 1 diabetic women. Diabetologia. 2009; 52: 160-168.

7. Fox H. The placenta in pregnancy hypertension. In: Rubin PC, ed. Handbook of hypertension, volume 10: hypertension in pregnancy. New York: Elsevier, 1988:16–37

8. Zhou Y, Damsky CH, Chiu K, Roberts JM, Fisher SJ. Preeclampsia is associated with abnormal expression of adhesion molecules by invasive cytotrophoblasts. J Clin Invest. 1993; 91: 950-960.

9. Zhou Y, Fisher SJ, Janatpour M, Genbacev O, Dejana E, Wheelock M, et al. Human cytotrophoblasts adopt a vascular phenotype as they differentiate. A strategy for successful endovascular invasion? J Clin Invest. 1997; 99: 2139-2151.

10. Cunningham FG, et al. Implantation, Placental Formation. In: Williams obstetrics. 23st ed. New York: McGraw-Hill, 2010: 36-77

11. Bischof P, Martelli M, Campana A, Itoh Y, Ogata Y, Nagase H. Importance of matrix metalloproteinases in human trophoblast invasion. Early Pregnancy. 1995; 1: 263-269.

12. Divya, Chhikara P, Mahajan VS, Datta Gupta S, Chauhan SS. Differential activity of cathepsin L in human placenta at two different stages of gestation. Placenta. 2002; 23: 59-64.

13. Fisher SJ, Leitch MS, Kantor MS, Basbaum CB, Kramer RH. Degradation of extracellular matrix by the trophoblastic cells of first-trimester human placentas. J Cell Biochem. 1985; 27: 31-41.

14. Fisher SJ, Cui TY, Zhang L, Hartman L, Grahl K, Zhang GY, et al. Adhesive and degradative properties of human placental cytotrophoblast cells in vitro. J Cell Biol. 1989; 109: 891-902.

15. Staun-Ram E, Goldman S, Gabarin D, Shalev E. Expression and importance of matrix metalloproteinase 2 and 9 (MMP-2 and -9) in human trophoblast invasion. Reprod Biol Endocrinol. 2004; 2: 59.

16. Yang Y, Yelavarthi KK, Chen HL, Pace JL, Terranova PF, Hunt JS. Molecular, biochemical, and functional characteristics of tumor necrosis factor-alpha produced by human placental cytotrophoblastic cells. J Immunol. 1993 Jun 15; 150: 5614-24.

17. Cohen M, Meisser A, Haenggeli L, Bischof P. Involvement of MAPK pathway in TNF-alpha-induced MMP-9 expression in human trophoblastic cells. Mol Hum Reprod. 2006; 12: 225-232.

18. Wiehler S, Cuvelier SL, Chakrabarti S, Patel KD. p38 MAP kinase regulates rapid matrix metalloproteinase-9 release from eosinophils. Biochem Biophys Res Commun. 2004; 315: 463-470.

19. Chapman HA. Plasminogen activators, integrins, and the coordinated regulation of cell adhesion and migration. Curr Opin Cell Biol. 1997; 9: 714-724.

20. Waltz DA, Natkin LR, Fujita RM, Wei Y, Chapman HA. Plasmin and plasminogen activator inhibitor type 1 promote cellular motility by regulating the interaction between the urokinase receptor and vitronectin. J Clin Invest. 1997; 100: 58-67.

21. Feng Q, Liu Y, Liu K, Byrne S, Liu G, Wang X, et al. Expression of urokinase, plasminogen activator inhibitors and urokinase receptor in pregnant rhesus monkey uterus during early placentation. Placenta. 2000; 21: 184-193.

22. Ostlund I, Haglund B, Hanson U. Gestational diabetes and preeclampsia. Eur J Obstet Gynecol Reprod Biol. 2004; 113: 12-16.

23. Schneider S, Freerksen N, Röhrig S, Hoeft B, Maul H. Gestational diabetes and preeclampsia--similar risk factor profiles? Early Hum Dev. 2012; 88: 179-184.

24. Vambergue A, Nuttens MC, Goeusse P, Biausque S, Lepeut M, Fontaine P. Pregnancy induced hypertension in women with gestational carbohydrate intolerance: the diagest study. Eur J Obstet Gynecol Reprod Biol. 2002; 102: 31-35.

25. Uddin MN, Horvat D, Roth AL, Pringle KG, Allen SR, Jones RO, Zawieja DC, Kuehl TJ. Hyperglycemia induces an anti-angiogenic milieu in first trimester cytotrophoblast cell. FASEB J April 9. 2013; 27: 835.5.

26. Uddin MN, Horvat D, Glaser SS, Mitchell BM, Puschett JB. Examination of the cellular mechanisms by which marinobufagenin inhibits cytotrophoblast function. J Biol Chem. 2008; 283: 17946-17953.

27. Vu HV, Ianosi-Irimie MR, Pridjian CA, Whitbred JM, Durst JM, Bagrov AY, et al. Involvement of marinobufagenin in a rat model of human preeclampsia. Am J Nephrol. 2005; 25: 520-528.

28. Agunanne E, Horvat D, Harrison R, Uddin MN, Jones R, Kuehl TJ, et al. Marinobufagenin levels in preeclamptic patients: a preliminary report. Am J Perinatol. 2011; 28: 509-514.

29. Uddin MN, Horvat D, Glaser SS, Danchuk S, Mitchell BM, Sullivan DE, et al. Marinobufagenin inhibits proliferation and migration of cytotrophoblast and CHO cells. Placenta. 2008; 29: 266-273.

30. Uddin MN, Horvat D, Childs EW, Puschett JB. Marinobufagenin causes endothelial cell monolayer hyperpermeability by altering apoptotic signaling. Am J Physiol Regul Integr Comp Physiol. 2009; 296: R1726-1734.

31. Agunanne EE, Uddin MN, Horvat D, Puschett JB. Contribution of angiogenic factors in a rat model of pre-eclampsia. Am J Nephrol. 2010; 32: 332-339.

32. Suwaki N, Masuyama H, Masumoto A, Takamoto N, Hiramatsu Y. Expression and potential role of peroxisome proliferator-activated receptor gamma in the placenta of diabetic pregnancy. Placenta. 2007; 28: 315-323.

33. Collino M, Aragno M, Mastrocola R, Gallicchio M, Rosa AC, Dianzani C, et al. Modulation of the oxidative stress and inflammatory response by PPAR-gamma agonists in the hippocampus of rats exposed to cerebral ischemia/reperfusion. Eur J Pharmacol. 2006; 530: 70-80.

34. Sweeney G, Somwar R, Ramlal T, Volchuk A, Ueyama A, Klip A. 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. J Biol Chem. 1999; 274: 10071-10078.

35. Nizamutdinova IT, Guleria RS, Singh AB, Kendall JA Jr, Baker KM, Pan J. Retinoic acid protects cardiomyocytes from high glucose-induced apoptosis through inhibition of NF-ÎºB signaling pathway. J Cell Physiol. 2013; 228: 380-392.

36. Kim SY, England L, Wilson HG, Bish C, Satten GA, Dietz P. Percentage of gestational diabetes mellitus attributable to overweight and obesity. Am J Public Health. 2010; 100: 1047-1052.

37. Nicholson W, Bolen S, Witkop CT, Neale D, Wilson L, Bass E. Benefits and risks of oral diabetes agents compared with insulin in women with gestational diabetes: a systematic review. Obstet Gynecol. 2009; 113: 193-205.

38. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes

mellitus on pregnancy outcomes. N Engl J Med. 2005; 352: 2477-2486.

39. Masuyama H, Nobumoto E, Segawa T, Hiramatsu Y. Severe superimposed preeclampsia with obesity, diabetes and a mild imbalance of angiogenic factors. Acta Med Okayama. 2012; 66: 171-175.

40. Sibai BM, Ewell M, Levine RJ, Klebanoff MA, Esterlitz J, Catalano PM, et al. Risk factors associated with preeclampsia in healthy nulliparous women. The Calcium for Preeclampsia Prevention (CPEP) Study Group. Am J Obstet Gynecol. 1997; 177: 1003-1010.

41. Reece EA, Sivan E, Francis G, Homko CJ. Pregnancy outcomes among women with and without diabetic microvascular disease (White's classes B to FR) versus non-diabetic controls. Am J Perinatol. 1998; 15: 549-555.

42. Siddiqi T, Rosenn B, Mimouni F, Khoury J, Miodovnik M. Hypertension during pregnancy in insulin-dependent diabetic women. Obstet Gynecol. 1991; 77: 514-519.

43. Combs CA, Rosenn B, Kitzmiller JL, Khoury JC, Wheeler BC, Miodovnik M. Early-pregnancy proteinuria in diabetes related to preeclampsia. Obstet Gynecol. 1993; 82: 802-807.

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