Preeclampsia and gestational diabetes mellitus: Pre-conception origins?

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Abstract
Preeclampsia (PE) and gestational diabetes mellitus (GDM) are two of the most common medical complications of pregnancy, with risks for both mother and child. Like many other antepartum complications, PE and GDM occur only in pregnancy. However, it is not clear if pregnancy itself is the cause of these complications or if these conditions are caused by factors that existed prior to gestation. In this paper, we hypothesize that although the clinical findings of PE and GDM are first noted during pregnancy, the origins of both conditions may actually precede pregnancy. We further hypothesize that pathophysiologic changes underlying PE and GDM are present prior to pregnancy, but remain undetected in the non-gravid state either because pregnancy is the trigger that makes these pathologies become clinically detectable or because there has been limited prospective longitudinal data comparing the pre-gravid and antepartum status of women that go on to develop these conditions. Rigorous prospective cohort studies in which women undergo serial systematic evaluation in the pre-conception period, throughout pregnancy and into the postpartum are ideally needed to test this hypothesis of pre-conception origins of PE and GDM. In this context, we are creating a pre-conception cohort, involving about 5000 couples who plan to have a baby within six months in Liuyang county in the Chinese province of Hunan. Results from this pre-conception cohort program should be able to provide definitive answer to the question of whether the underpinnings of PE and GDM originate prior to pregnancy. Ultimately, the significance of addressing this hypothesis is underscored by its potential implications for targeted interventions that could be designed to (i) prevent the deleterious effects of PE/GDM and (ii) thereby interrupt the vicious cycle of disease that links affected women and their offspring.

Introduction
Preeclampsia (PE) and gestational diabetes mellitus (GDM) are two common complications in pregnancy, affecting more than 10% pregnancies worldwide [1–4]. Numerous studies have been conducted in the past four decades on these two important pregnancy complications, and much progress has been made. It is now quite clear that, while these two conditions have distinctive clinical and pathophysiologic characteristics, they share some important similarities: both conditions develop during pregnancy and the clinical syndromes disappear after delivery; many risk factors such as obesity, elevated blood pressure, dyslipidemia, insulin resistance, and hyperglycemia, are associated with both PE and GDM; and patients with a history of PE or GDM have increased risk of developing cardiovascular disease as compared to women without such a history [1–22]. However, the true underlying causes of these two conditions remain to be fully elucidated. Although both conditions are first diagnosed during pregnancy, it is uncertain whether they originate prior to or during pregnancy. In this paper, we consider current understanding of the clinical and pathophysiologic features of PE and GDM. Based on our synthesis of these data, we propose the hypothesis that the underpinnings of both PE and GDM originate prior to pregnancy. Finally, we present preliminary evidence to support the pre-conception origins hypothesis and discuss its potential implications for the prevention and management of these two pregnancy complications.
Clinical and pathophysiologic characteristics of preeclampsia and gestational diabetes mellitus

Clinical and pathophysiologic characteristics of preeclampsia

PE is defined as hypertension and proteinuria that develop during pregnancy [1]. PE is a leading cause of maternal and neonatal morbidity and mortality [5]. Indeed, it accounts for about one-third of maternal deaths, ranking second among causes of pregnancy associated deaths in industrialized countries [6]. Pathological changes in renal and liver function and vascular, haematological, neurologic and cerebral systems occur in women with PE; while seizures and HELLP (hemolysis, elevated liver enzymes, low platelets) syndrome can occur in more severe forms of this condition [1]. Since delivery is the only known cure, PE is a leading cause of indicated preterm delivery [23]. In a study by Peek et al., women with mild and severe PE had mean gestational ages of 38.3 and 35.3 weeks, respectively (as compared to 39–40 weeks in the general population), and their respective perinatal mortality rates were 2% and 4% (as compared to 5–6 per 1000 in the general population) [24]. PE accounts for 25% of very low birth weight infants [25] and as many as 60% of these infants suffer from learning disabilities and low IQ [26]. According to our analysis of the perinatal database in the Canadian province of Ontario, the provincial cost of caring for extremely low birth weight infants in the first two years of life attributable to PE was an estimated $19 million in 2005 [27].

Furthermore, although the clinical syndrome of PE disappears after delivery, women with a history of this condition continue to be at risk for future cardiovascular events [17,18]. Women affected by PE have an increased prevalence of vascular risk factors [28], including the metabolic syndrome [19] which is an established predictor of future cardiovascular disease [20]. PE potentially may also increase the risk of cardiovascular disease in the offspring through ‘fetal origins of adult diseases’ [21,22].

Because the clinical syndromes of PE disappear after the delivery of the placenta, investigators have focused on the placental pathology in the study of PE pathophysiology [1]. The current paradigm of the pathophysiology of PE is that it is likely a two-stage disorder: at stage I (likely at late first trimester or early second trimester), there is a decrease in placental perfusion, which is secondary to abnormal migration of trophoblasts into maternal spiral arteries; and, at stage II (typically early third trimester), the maternal syndrome of PE, which is secondary to systemic endothelial dysfunction (including impairment of the nitric oxide system, overactivity of the autonomic nervous and/or renin–angiotensin systems, activation of a systemic inflammatory response, and activation of circulating proteins that interfere with angiogenesis) [5,29,30]. Roberts has hypothesized that substances produced by the poorly perfused placenta enter the systemic circulation and alter endothelial cell activity (8). This effect has been thought to change vascular sensitivity to circulating pressors, activate coagulation, and reduce vascular integrity, resulting in the pathophysiologic changes of PE [8].

Clinical and pathophysiologic characteristics of gestational diabetes mellitus

GDM, defined as glucose intolerance of varying severity with first onset and recognition in pregnancy, is a common disorder affecting between 3% and 14% of pregnancies [2–4]. As with PE, it is a diagnosis that holds both immediate implications in pregnancy and long-term medical risks. Indeed, although their hyperglycemia typically resolves in the early postpartum, women with GDM have a very high risk of ultimately developing type 2 diabetes (T2DM), on the order of 20–50% within 5 years after delivery [31,32]. Besides T2DM, women with a history of GDM are at risk of developing several other traditional cardiovascular risk factors, including hypertension, dyslipidemia, obesity, and metabolic syndrome [3,9–15]. Importantly, this constellation of vascular risk factors contributes to an increased risk of cardiovascular disease in women with GDM. Notably, despite their relative youth (i.e., childbearing age), women with GDM have a 70% higher incidence of cardiovascular disease compared to their peers, within just 11 years following the index pregnancy [16]. Since cardiovascular disease represents the clinical manifestation of a slow pathologic process (atherosclerosis) that occurs over years to decades, it is believed that women with GDM have a long-standing (and typically clinically unrecognized) exposure to cardiovascular risk factors, which precedes their presentation with overt vascular disease [33].

While affected women have an increased risk of developing T2DM and cardiovascular disease in the years to come, the most pressing concern at the time of diagnosis is that GDM is associated with an increased risk of adverse obstetrical outcomes, including macrosomia, shoulder dystocia, birth injury, prematurity, perinatal mortality, and the need for caesarean section [2,4]. The common feature underlying these risks is fetal overgrowth, which may be partly driven by maternal hyperglycemia. Specifically, maternal hyperglycemia leads to fetal hyperglycemia, which stimulates fetal insulin secretion. While the metabolic effects of this insulin secretory response will lower blood glucose levels in the fetus, the concomitant anabolic effects of insulin can cause excessive fetal growth. First proposed by Pedersen in 1951 [34], this model of fuel-mediated macrosomia has since been supported through the work of numerous investigators and is well-accepted as the basis for macrosomic risk in diabetes in pregnancy [35,36]. Thus, a fundamental goal of management in women with GDM is the control of maternal glyemia in order to reduce the likelihood of fetal overgrowth. Accordingly, it is now standard obstetrical practice for all pregnant women to be screened for GDM in late 2nd trimester, with those so identified treated with glucose-lowering therapy (lifestyle modification ± insulin, if needed) towards the goal of normalizing maternal glucose levels.

Though the protocols for GDM screening vary across institutions, common elements are (i) their typical timing in late 2nd trimester and (ii) the use of dynamic testing in response to an oral glucose challenge (such as a screening glucose challenge test or a diagnostic oral glucose challenge test). The consistency of these two elements partly relates to the pathophysiology of GDM. Specifically, in response to the normal physiologic progressive decline in whole-body insulin sensitivity that occurs from mid-pregnancy onwards, the pancreatic beta-cells must proportionately increase their secretion of insulin for normal glucose homeostasis to be maintained [2,37]. GDM arises in a population of women who have a chronic defect in beta-cell function such that they are unable to secrete sufficient insulin to fully compensate for this acquired insulin resistance of late pregnancy, resulting in the hyperglycemia by which GDM is diagnosis [2,37]. Thus, screening for GDM typically involves an oral glucose challenge to test the efficiency of the insulin secretory response of the beta-cells in the context of the insulin resistance that arises after mid-gestation. Although this pathophysiology and approach to screening have led to the general belief that GDM only develops in the latter half of pregnancy, several lines of emerging evidence suggest that affected women may differ from their peers long before their diagnosis with this disorder.

Hypothesis: the pre-conception origins of preeclampsia and gestational diabetes mellitus

We hypothesize that although, the clinical findings of PE and GDM are first noted during pregnancy, the underpinnings of both conditions may originate prior to pregnancy. We further hypothe-
size that pathophysiologic changes underlying PE and GDM are present prior to pregnancy, but remain undetected in the non-gravid state either because pregnancy is the trigger that makes these pathologies become clinically detectable or because there has been limited prospective longitudinal data comparing the pre-gravid and antepartum status of women that go on to develop these conditions.

**Evidence to support the hypothesis of pre-conception origins of preeclampsia**

PE shares many risk factors with cardiovascular disease such as hypertension, obesity, insulin resistance, endothelial dysfunction, hyperuricemia, and hyperhomocysteinemia [7]. As data has accumulated, it has become increasingly evident that the insult to the endothelium by materials produced by the poorly perfused placenta is neither toxicity nor a nonspecific injury but rather may be better characterized as endothelial activation. It seems likely that the responsible agent(s) are not unique molecules but rather usual molecules present in excessive amounts or in the setting of enhanced sensitivity to their bio-activity [8]. As a result, the hypothesis has been expanded to include the maternal generation of endothelial injury and injuries [8]. This concept is perpetuated by the observations that reduced placental perfusion is not sufficient to generate the maternal syndrome of PE, that women with growth-restricted fetuses frequently are not preeclamptic, and that placental bed biopsies from not only growth-restricted but also premature infants demonstrate failure of the physiologic remodeling of decidual vessels responsible for the reduced placental perfusion of PE [8]. These observations have led to the concept that PE is secondary to an interaction of reduced placental perfusion and pre-existing maternal factors. In this context, the pre-gravid status of women who go on to develop PE is of interest; however, little is known in this regard.

Similarly, it remains unclear whether PE arises in women with an underlying susceptibility for future cardiovascular disease or if the development of PE itself potentiates vascular risk in later life. For example, through potential mechanisms of renal damage, PE may independently increase the risk of long-term cardiovascular morbidity and mortality. However, because previous studies have assessed the risk factors for PE and cardiovascular disease in adult life separately, it is not known if the development of PE itself potentiates future vascular risk after childbirth, or if risk factors that already existed prior to pregnancy actually predisposed these women to higher risk of subsequent cardiovascular disease. Indeed, very few studies have actually compared the pre-pregnancy and pregnancy status of the same woman in terms of PE risk or related issues [38,39]. With respect to the latter, Brackley et al. studied vascular function by Doppler assessment in a cohort of 17 healthy women every four weeks from early pregnancy until term and up to three months postpartum (including 10 subjects with pre-conception data). In addition to a dramatic eight-fold increase in downstream resistance within the external iliac artery in the second half of pregnancy, they noted that blood pressure falls in the first half of pregnancy before subsequently rising [38]. These vascular changes in healthy women underscore the need for similar longitudinal data spanning the time course from pre-conception, across gestation and into the postpartum in women that develop PE, to see if they may differ from their peers either before pregnancy or in the changes that take place between pre-pregnancy and early gestation.

**Evidence to support the hypothesis of pre-conception origins of gestational diabetes mellitus**

There are three key lines of evidence suggesting that metabolic dysfunction may precede the diagnosis of GDM. Firstly, several studies have now shown that, compared to their peers, women who go on to develop GDM later in pregnancy have biochemical abnormalities that can be detected in the 1st trimester. These abnormalities include (i) higher fasting glucose, (ii) greater insulin resistance, (iii) lower circulating levels of the fat-derived protein adiponectin, (iv) increased inflammation (as indicated by C-reactive protein (CRP) and leukocyte count), (v) dyslipidemia (higher triglycerides and lower levels of high-density-lipoprotein (HDL) cholesterol), (vi) low sex-hormone-binding globulin (SHBG), (vii) lower stores of vitamins D and C, and (viii) increased levels of tissue plasminogen activator (t-PA) antigen, leptin and uric acid [40–51]. While the independent contributions of these inter-related factors remain to be determined, the salient point is that their detection in the first trimester can predict subsequent GDM, long before its clinical manifestation as hyperglycemia in the setting of the severe insulin resistance of late pregnancy.

Secondly, these early pregnancy abnormalities may influence the intrauterine environment before GDM is even diagnosed. Indeed, it has recently been demonstrated that fetal exposure to altered levels of amniotic fluid glucose, insulin and insulin-like growth factor-binding protein-1 (IGFBP-1) can be detected by 15 weeks’ gestation in women that go on to develop GDM [52]. Thus, when glucose-lowering treatment for GDM is initiated at the time of diagnosis in late 2nd trimester, deleterious consequences of fetal exposure to intrauterine metabolic perturbations may have already taken place. In this regard, it is of interest to note that clinical trials have generally not shown that treatment of GDM reduces the risk of individual adverse obstetrical outcomes (such as macrosomia, cesarian section, birth trauma, and perinatal mortality) [53], although the two largest such trials and a recent meta-analysis all reported lower rates of shoulder dystocia [53–55]. While this limited evidence of treatment efficacy may suggest that current glucose-lowering therapy alone is insufficient to reduce adverse obstetrical outcomes, an alternative possibility is that the deleterious fetal effects of maternal metabolic dysregulation may have occurred prior to the diagnosis of GDM and hence cannot be fully prevented by subsequent treatment. Further to this point, it is of interest that, in women without GDM, glucose levels at the time of glucose tolerance testing in late 2nd trimester have been associated with epigenetic modification of the fetal leptin gene [56], suggesting at least one mechanism whereby mild metabolic perturbation prior to GDM screening may affect metabolic function in the developing fetus [57]. The potential significance of such an effect is further underscored by the fact that several studies have shown that the offspring of women with GDM develop an early enhanced cardio-metabolic risk factor profile in childhood and adolescence, as compared to the peers [58–64].

The third line of evidence suggesting that chronic dysfunction may precede the diagnosis of GDM pertains to the postpartum status of affected women. In the immediate postpartum, the severe acquired insulin resistance of late pregnancy resolves and women with GDM typically regain normal glucose tolerance. However, they continue to exhibit metabolic abnormalities, as compared to their peers, including greater insulin resistance and pancreatic beta-cell dysfunction [65–68]. Indeed, in the years after delivery, progressive worsening of this beta-cell dysfunction against a background of chronic insulin resistance is believed to be the pathophysiologic mechanism underlying the elevated risk of developing T2DM in women with previous GDM [69–73]. Furthermore, even by as early as 3 months postpartum, women with recent GDM show an enhanced cardio-metabolic risk factor profile, as compared to the general obstetric population, including both (i) traditional risk factors, such as pre-diabetes/diabetes, hypertension, elevated low-density-lipoprotein (LDL) cholesterol, hypertriglyceridemia, low levels of HDL cholesterol, and metabolic syndrome, and (ii) novel non-traditional risk factors, such as in-
increased CRP and low circulating levels of adiponectin [3,14,15,74–76]. While chronic exposure to these risk factors is believed to contribute to the increased future risk of CVD in women with GDM [16,33], it is of interest that this enhanced risk factor profile is apparent so soon after delivery. Indeed, the presence of these cardio-metabolic risk factors in the early postpartum, coupled with their earlier detection in first trimester (discussed above), raises the intriguing possibility that these abnormalities may have preceded the pregnancy itself. Thus, taken together, these data may point to pre-conception origins of GDM.

To date, there has been limited study of pre-gravid function of women who go on to develop GDM. These limited data, however, do support the concept of metabolic dysfunction prior to pregnancy in this patient population. Of note, women that develop GDM are believed to have chronic insulin resistance and chronic beta-cell function that precedes the index pregnancy [2,77,78]. Accordingly, pre-gravid glucose levels predict GDM [78,79]. Furthermore, in women without a family history of diabetes, low HDL cholesterol prior to pregnancy has been associated with subsequent GDM [78]. Similarly, in women with polycystic ovarian syndrome, those with low pre-gravid levels of SHBG have an increased risk of GDM [80]. Finally, maternal obesity, hypertension, and lower levels of physical activity prior to pregnancy have been shown to predict the development of GDM [79,81,82]. Taken together, these data support the hypothesis that the origins of GDM may lie prior to conception.

Implications of the pre-conception origins hypothesis

If confirmed by large-scale prospective longitudinal studies, our hypothesis that PE and GDM originate from susceptibilities that exist prior to pregnancy will provide insight relevant to a fundamental question in medical science: is the gravid state itself the cause of many complications that are observed only in pregnancy or are there pre-existing factors in women who eventually develop these complications? Moreover, this hypothesis will have important practical implications relevant to the prevention and management of PE and GDM.

Implications of this hypothesis for the prevention and management of preeclampsia

Early detection of disease theoretically can help physicians in achieving optimal management. As a result, many studies have been carried out in the past to search for biomarkers that can serve as prediction tools. A major obstacle in the search for biomarkers of pregnancy complications such as PE is the variability of the candidate biomarkers in pregnancy. Factors that may introduce variability in the measured levels of candidate biomarkers include (i) differences in metabolism before and after pregnancy or between different periods of gestation, (ii) nutrient consumption by the growing fetus, and (iii) other physiologic and/or pathological changes that occur in pregnancy [83]. For example, recent studies suggest that soluble endoglin (sEng) may be a useful biomarker for early detection of PE [84–89]. Indeed, Kana et al. observed that, for women who developed preterm PE (<37 weeks), the difference (delta[d]) between second and first trimester levels of sEng (dsEng) was 0.73 ± 0.77 ng/mL, as compared to −1.32 ± 0.18 ng/mL in normotensive women [86]. These data suggest that sequential changes in sEng could provide a means for early detection of PE. The pre-conception origins hypothesis raises the possibility that pre-gravid sEng and its subsequent changes in pregnancy may provide even earlier detection of women who are at risk of developing PE when pregnant.

The pre-conception origins hypothesis may have important implications in the prevention of PE as well. For example, previous studies have suggested that folic acid supplementation during pregnancy may have a protective effect on PE [90–92]. According to our pre-conception hypothesis, pre-gravid folic acid may be relevant to the development of PE. Though pre-conception folic acid supplementation is a recommended therapy to reduce the risk of neural tube defects [93], its relevance to risk of PE or the appropriate dose in that context is not known. Nevertheless, the pre-conception origins hypothesis raises the possibility that preventive therapy to reduce the risk of PE could be implemented prior to pregnancy, particularly in those women with identified risk factors or biomarkers.

Implications of this hypothesis for the prevention and management of gestational diabetes

A demonstration that its origins arise prior to conception would also have important implications in the prevention and management of GDM. For example, if pre-conception insulin resistance predicts future GDM, then its assessment (which can be achieved very simply through fasting measurement of blood glucose and insulin) can be used to identify at-risk women prior to pregnancy. Randomized controlled trials could then be undertaken to see if pre-gravid treatment with insulin-sensitizing therapies (such as weight loss and metformin) could prevent the development of GDM in at-risk women. The importance of pre-gravid prevention is underscored by the recent recognition that, in women who go on to develop GDM, intrauterine metabolic abnormalities are present long before their clinical diagnosis with GDM [52]. Furthermore, such prevention potentially could reduce the cardio-metabolic risk that ultimately manifests in the offspring of GDM pregnancies.

Secondly, by focusing attention on the pre-gravid state, this hypothesis may lead to the identification of novel bio-markers for stratifying women according to their future risk of GDM. Such bio-marker evaluation may suggest therapeutic targets for risk modification. For example, if decline in circulating levels of the fat-derived protein adiponectin from pre-conception to early pregnancy is associated with later GDM, then randomized controlled trials could be considered to see if pre-gravid treatment to raise adiponectin levels (e.g. by weight loss or thiazolidinedione) [94,95] can prevent GDM.

Thirdly, the pre-conception origins hypothesis will hold implications for the clinical management of cardio-metabolic risk in women with GDM or PE. For example, if the cardio-metabolic risk factor profile observed in the postpartum following GDM or PE is actually present prior to pregnancy, then pre-gravid risk factor modification (such as aggressive blood pressure and lipid control) may be warranted in women at risk of GDM/PE in order to reduce their long-term cardiovascular morbidity and mortality. Alternatively, if the post-delivery risk factor profile is a result of the GDM/PE pregnancy, then only postpartum intervention needs to be considered.

Conclusions

To date, there has been limited study of pre-gravid function of women who go on to develop PE and GDM. Limitations of these studies include retrospective assessment of pre-pregnancy characteristics, modest sample sizes, incomplete covariate adjustment, and a lack of prospective ascertainment of blood pressure and glucose tolerance status in pregnancy [38,39,77–81]. Thus, rigorous prospective cohort studies in which women undergo serial systematic evaluation in the pre-conception period, throughout preg-
nancy and into the postpartum are ideally needed to test the hypothesis of pre-conception origins of PE and GDM. In this context, we are now establishing such a pre-conception cohort, involving about 5000 couples who plan to have a baby within six months in the Chinese province of Hunan. Results from this pre-conception cohort program should be able to provide definitive answer to the question of whether the underpinnings of PE and GDM originate prior to pregnancy. Ultimately, the significance of addressing this hypothesis is underscored by its potential implications for targeted interventions that could be designed to (i) prevent the deleterious effects of PE/GDM and (ii) thereby interrupt the vicious cycle of disease that links affected women and their offspring.

Conflicts of interest statement

None declared.

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