# Diabetes and pre-eclampsia affecting pregnancy: a retrospective cross-sectional study

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## ABSTRACT

The interaction between pre-eclampsia and diabetes mellitus (DM) is far from being completely understood. In this study, we compared normal pregnancies with those complicated with pre-eclampsia, gestational DM, and/or pre-existing diabetes to assess the effects of hyperglycemia on placental development. AnInstitutional Review Board (IRB) approved retrospective cross-sectional study with 621 subjects was performed. Statistical analysis was performed using Duncan's post hoc test and analysis of variance. Regardless of diabetes status, patients with pre-eclampsia delivered prematurely. Patients in the group with pre-eclampsia and pregestational diabetes delivered much earlier, at 35.0±0.4 weeks, when compared with the patients that had pre-eclampsia with gestational diabetes and pre-eclampsia with no diabetes (*P<0.05 for each). Additionally, patients with pre-existing diabetes who developed pre-eclampsia delivered smaller babies than those with pre-existing diabetes without pre-eclampsia (1.00±0.03, P<0.05 for each). Pre-existing diabetes with added insult of pre-eclampsia led to fetal growth restriction. This outcome validates the understanding that elevated glucose earlier in pregnancy alters placentogenesis and leads to fetal growth restriction.

### Significance of this study

**What is already known about this subject?**

- The topic of diabetes and pre-eclampsia affecting pregnancy, along with clinical outcomes, has been previously discussed.
- The effect of high maternal blood glucose in placentogenesis has been very well established. Our lab contributed to this subject as well.
- The clinical outcomes secondary to a combination of maternal diabetes and pre-eclampsia in newborn infants are not very well established.

**What are the new findings?**

- The authors concluded from this research that infants born to a mother affected with a combination of pre-eclampsia and diabetes mellitus have higher morbidity compared with infants born to a mother affected by either pre-eclampsia or diabetes alone. This is likely due to increased maternal blood glucose levels altering the placentogenesis.
- The authors found that pregestational diabetes increases the risk of morbidity in newborn babies when compared with gestational diabetes alone with or without pre-eclampsia.
- Infants born to women with pregestational diabetes and pre-eclampsia had more complications and extended hospital stay.

## INTRODUCTION

Diabetes mellitus (DM) is the most common pre-existing endocrine disorder in pregnancy. Its prevalence will likely continue to rise as the average age of onset of diabetes is falling throughout the general population.[1] By the year 2030, more than 360 million people worldwide could potentially have DM, which would pose a challenge for clinicians to manage more pregnancies complicated by the condition.[2] Diabetes during pregnancy can be pre-existing diabetes (women with previously diagnosed type 1 or type 2 diabetes) and gestational DM (GDM), which is defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[3 4] Approximately 7% of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually. Increased long-term risk of developing type 2 DM in the mother and the offspring is linked to the development of GDM during pregnancy.[5–7]

Maternal diabetes, whether gestational or pre-existing, contributes to an unfavorable environment for embryonic and fetal-placental development. Many recent advances in diabetes research have contributed to increased understanding of the pathophysiology of the disease, improved management, and decreased morbidity and mortality in pregnancies complicated by diabetes.[1] In spite of all the recent advances in the management, pregnant women with diabetes are at an increased risk for unfavorable perinatal outcomes. The risk of congenital malformations, maternal-fetal complications, placental abnormalities, and intrauterine malprogramming is much higher

## Significance of this study

**How might these results change the focus of research or clinical practice?**

- Through this retrospective study, we found that pregestational diabetes has more detrimental effects on the fetus and newborn when compared with gestational diabetes with or without pre-eclampsia. We do not know the reason for this, but we speculate that increased maternal blood glucose levels affect the placental angiogenesis with pre-eclampsia being an added insult. A prospective study is warranted to assess a cause and effect relationship, and we are currently working on that project. We conclude that women who are pregnant with pregestational diabetes and pre-eclampsia will need closer clinical and laboratory monitoring for fetomaternal well-being.

in diabetic mothers. Maternal complications including hypertension, pre-eclampsia, and/or a cesarean section are common. Furthermore, risks to the fetus include macrosomia, intrauterine growth restriction, shoulder dystocia, hypoglycemia, and respiratory distress.[3]

Pre-eclampsia affects 3%–10% of pregnancies and is a leading cause of maternal and fetal morbidity and mortality, accounting for nearly 60,000 maternal deaths per year worldwide.[8–11] Pregnant women presenting with new onset hypertension alongside proteinuria or severe organ dysfunction during the second half of pregnancy are diagnosed with pre-eclampsia. The American Congress of Obstetricians and Gynecologists (ACOG) has said that the pre-eclampsia can be diagnosed in the absence of proteinuria in hypertensive pregnant women with end organ dysfunction.[12] Pre-eclampsia is often accompanied by significant edema, intrauterine growth restriction, and neurologic complications such as cortical blindness, aphasia, weakness, paralysis and cerebral vascular accidents, and the potential progression to seizures (eclampsia) along with many long-term health implications for both the mother and offspring.[13 14] According to the American Heart Association, the women with pre-eclampsia are at increased risk for future cardiovascular disease and stroke compared with the general population,[12] and the offspring of these women will have lifelong adverse cardiovascular consequences.[14]

General understanding of the etiologies of both DM and pre-eclampsia is growing, but many aspects of the pathophysiology and interaction between the disease processes remain unclear.[15–17] The two conditions share many common risk factors that make it difficult to tease out the exact causes and effects each disease process has on the other. However, many reproducible and reliable studies have shown a significant association between GDM and pre-eclampsia that is independent of common risk factors.[18] Pre-existing diabetes increases the risk of pre-eclampsia fourfold. The risk of pre-eclampsia is also increased by GDM, although it is unclear whether these two conditions share a common pathophysiological pathway. In addition, non-diabetic women who have had pre-eclampsia are more likely to develop type 2 diabetes later in life. Among women with type 1 diabetes, a history of pre-eclampsia is associated with an increased risk of retinopathy and nephropathy. As investigators learn more about the important interplay between these two disease processes, it is clear that more research examining the pathophysiology, treatment, and outcomes of pre-eclampsia among women with pre-existing and gestational diabetes is needed.

### Hypothesis

The objective of this study was to compare normal pregnancies to those complicated with pre-eclampsia in patient groups with no diabetes, with gestational diabetes and those with pre-existing DM in order to assess different pregnancy outcomes within each group. More specifically, we aimed to learn more about the effect of hyperglycemia on placental development and its role in the pathogenesis of pre-eclampsia.

## METHODS

### Study design and patient population

This is a retrospective cross-sectional study performed after receiving Institutional Review Board (IRB) approval. A total of 621 subjects with a live singleton delivery were randomly selected from the year 2008 through 2011 at the Scott and White Memorial Hospital in Temple, Texas, USA. Out of 621 subjects, 350 did not have any diabetes or pre-eclampsia, 118 had pre-eclampsia but no diabetes, 72 had GDM but no pre-eclampsia, 23 had GDM and pre-eclampsia, 21 had pre-GDM but no pre-eclampsia, and 37 had both pre-GDM and pre-eclampsia. The average age of patients who had pre-eclampsia ranged from 26.9 years to 31.6 years, while the average age of patients who had diabetes ranged from 27.6 years to 28.1 years. None of the patients had chronic hypertension, and only six were tobacco smokers.

At our institution, gestational diabetes is diagnosed by using a two-step oral glucose tolerance test. During the first step, a 50 gm glucose challenge given at 24–28 weeks gestation as a screening test, followed by a 3-hour 100 gm glucose tolerance test if the patient failed the screening test. Diabetics were treated with dietary modifications, oral hypoglycemic drugs (metformin, glyburide) and insulin according to the severity. Traditionally, pre-eclampsia is diagnosed with presence of hypertension and proteinuria. Blood pressures were measured in our subjects at the time of diagnosis of pre-eclampsia, which is after 20 weeks of gestation. At Baylor Scott and White, we diagnose pre-eclampsia based on the guidelines from ACOG. According to ACOG, pre-eclampsia may be diagnosed in the absence of proteinuria in hypertensive pregnant women with end organ involvement such as pulmonary edema, progressive renal failure, impaired liver function, thrombocytopenia, new onset cerebral disturbances, or visual disturbances.[12] The institutional policy on delivery of the pregnant women with pre-eclampsia states that delivery should take place at around 37 weeks in case of mild pre-eclampsia and around 34 weeks in case of severe pre-eclampsia. Similarly, in case of maternal diabetes (pre-GDM and GDM), delivery takes place between 34 weeks and 39 weeks of gestation if the diabetes is poorly controlled. If the diabetes is well controlled, the patient is treated as a normal pregnant woman.[19]

**Table 1** Patient age in years (mean±SE, N) at delivery varied (P<0.0001 using ANOVA)

| Diabetes group | No PreE | Developed PreE |
|---|---|---|
| No gestational diabetes | 26.0±0.3, 351[A] | 26.9±0.5, 118[A] |
| Diabetes mellitus prior to pregnancy | 27.6±1.3, 21[A] | 31.6±1.0, 37[B] |
| Developed gestational diabetes mellitus | 28.1±0.7, 72[A] | 31.3±1.2, 23[B] |

Groups with difference letter superscripts (A and B) differed (P<0.05 using Duncan's post hoc test).
ANOVA, analysis of variance; PreE, preeclampsia.

## Data collection and statistical analysis

Maternal age, blood pressures, gestational age at delivery, and infant birth weight were collected. Statistical analysis was performed using Duncan's post hoc test and analysis of variance (ANOVA). The authors needed to examine birth weight while adjusting for varying gestational age at birth. The relationship of gestational age with birth weight in normal pregnancies was used for adjustment. Average birth weight for the normal pregnancy group without diabetes and pre-eclampsia =3222 gm (616 gm SD) so that each 1% change =32 gm.

## RESULTS

Patients who did not develop pre-eclampsia showed no significant difference in mean age regardless of diabetes status. Women who had pre-existing DM or GDM that went on to develop pre-eclampsia were older on average than non-diabetic patients with pre-eclampsia. The difference in each patient's age in years (mean ±SE, N) at delivery varied (P<0.0001 using ANOVA) in pre-eclampsia versus non-preeclamptic groups. As maternal age increases, the risk of having pre-existing diabetes or developing GDM increases. This phenomenon increases further to a significant degree in those with pre-eclampsia (table 1). Despite null parity being a risk factor for both GDM and pre-eclampsia, our results did not show significant difference among groups for gravidity (P=0.21, using ANOVA), with the average gravidity of 2.7 (1.8 SD) for 621 subjects having a range of 1 to 14 pregnancies. Patients with pre-eclampsia had increased blood pressures for both systolic and diastolic pressures regardless of their diabetes status. Their systolic and diastolic blood pressures (mean ±SE, N) varied (P<0.0001 using ANOVA) (table 2), and they delivered prematurely compared with those without pre-eclampsia, again regardless of diabetes status. The difference in gestational age in weeks (mean ±SE, N) at delivery varied (P<0.0001 using ANOVA) between the two groups. Patients with pre-eclampsia delivered earlier in pregnancy; the women with pre-existing diabetes delivered even earlier than those in the other two pre-eclampsia groups, suggesting a more severe condition (table 3). After adjusting birth weight for gestational age, there was a 4% (about 128 gm) reduction in birth weight in those with pre-eclampsia alone, which was not a significant difference for this sample size. The diabetic women, regardless of pre-eclampsia, delivered babies that were larger than average compared with normal pregnancies (with one notable exception). Those with pre-existing diabetes who developed pre-eclampsia did not deliver the expected large for gestational age babies, but rather resulted in babies that were comparable in weight to those with normal pregnancies. The authors used this relationship to normalize birth weight for the gestational age of all groups, as groups did differ in gestational age at birth (figure 1). The effect of pre-eclampsia in pregnancies without diabetes is to reduce birth weight for gestational age by 4% or about 128 gm. This difference was not significant for this sample size (table 4). Diabetes prior to the onset of pregnancy leads to larger babies at

**Table 2** Patient blood pressures in mm Hg (mean±SE, N) for systolic/diastolic varied (P<0.0001 using ANOVA)

| Diabetes group | No PreE | Developed PreE |
|---|---|---|
| No gestational diabetes | 121±1, 344[A]<br>72±1, 344[A] | 152±1, 118[B]<br>87±1, 118[B] |
| Diabetes mellitus prior to pregnancy | 119±3, 16[A]<br>74±3, 16[A] | 156±2, 37[B]<br>89±2, 37[B] |
| Developed gestational diabetes mellitus | 124±2, 64[A]<br>72±1, 64[A] | 154±3, 23[B]<br>91±2, 23[B] |

Groups with difference letter superscripts (A and B) differed (P<0.05 using Duncan's post hoc test).
ANOVA, analysis of variance; PreE, preeclampsia.

**Table 3** Patient gestational age weeks (mean±SE, N) at delivery varied (P<0.0001 using ANOVA)

| Diabetes group | No PreE | Developed PreE |
|---|---|---|
| No gestational diabetes | 38.7±0.1, 351A | 36.7±0.2, 118B |
| Diabetes mellitus prior to pregnancy | 37.5±0.6, 21A | 35.0±0.4, 37C |
| Developed gestational diabetes mellitus | 38.1±0.3, 72A | 36.7±0.5, 23B |

Groups with difference letter superscripts (A and B) differed (P<0.05 using Duncan's post hoc test).
ANOVA, analysis of variance; PreE, preeclampsia.

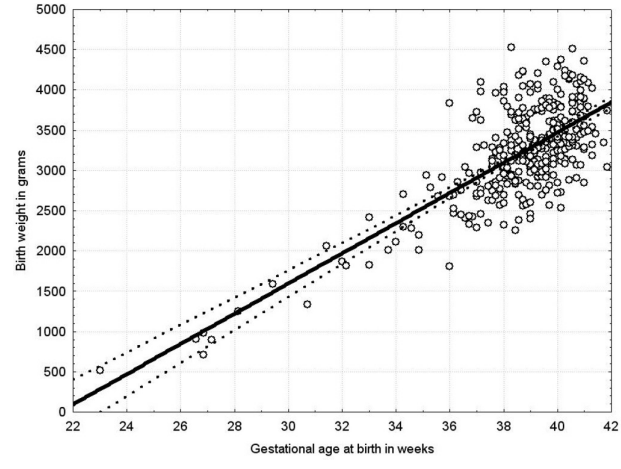


**Figure 1** Patient birth weight (kg) normalized for gestational age in weeks for normal pregnancies (mean±SE, (N) varied (P<0.0001 using ANOVA). As gestational age at birth varied, there was a need to examine birth weight after adjustment for gestational age. The authors used the relationship of gestational age with birth weight in normal pregnancies for adjustment. Birth weight normalized for the gestational age at birth. ANOVA, analysis of variance.

**Table 4** Patient birth weight normalized for gestational age in weeks (mean±SE, N) varied (P<0.0001 using ANOVA). Note that the normalized birth weight for pregnancies without diabetes and PreE throughout the pregnancy did not differ from 1

| Diabetes group | No PreE | Developed PreE |
|---|---|---|
| No gestational diabetes | 1.00±0.01, 351[A] | 0.96±0.01, 118[A] |
| Diabetes mellitus prior to pregnancy | 1.16±0.4, 21[B] | 1.00±0.03, 37[A] |
| Developed gestational diabetes mellitus | 1.07±0.02, 72[A,B] | 1.09±0.03, 23[B] |

Groups with difference letter superscripts (A and B) differed (P<0.05 using Duncan's post hoc test).
ANOVA, analysis of variance; PreE, preeclampsia.

delivery than in normal pregnancies, and pre-eclampsia in this subset of pregnancies was associated with reduced birth size that was not different from normal pregnancies. However, development of gestational diabetes did not cause intrauterine growth restriction in pregnancies with pre-eclampsia. Interestingly, although babies of patients with DM prior to pregnancy who developed pre-eclampsia were not small for gestational age, they were smaller than those from pregnancies with only prior DM. This suggests that the pre-eclampsia in these pregnancies did lead to growth restriction. On the other hand, this difference was not seen in pregnancies where DM developed during the pregnancy, typically assessed at 24 weeks to 28 weeks gestation. This supports the concept that elevated blood glucose levels in the first trimester of pregnancy may alter placental development, leading to fetal growth restriction later in pregnancy when a second hit triggers pre-eclampsia.

## DISCUSSION

Many of the findings in the current study were well aligned with well known risk factors and outcomes of pre-eclampsia and DM. Women with pre-eclampsia have previously been shown to have significantly higher rates of preterm delivery (<37 weeks gestation),[14] which correlates with the findings in this study. Many studies have also clearly established that women of advanced maternal age (≥35 years) or high maternal age (≥40 years) are significantly more likely to have pre-existing medical disorders such as DM or hypertension.[15 20 21] Nationwide US data suggest that the risk of pre-eclampsia increases by 30% for every additional year of age past 34 years.[22] The results of this study similarly demonstrate that, as maternal age increases, the risk of having pre-existing diabetes or developing GDM increases, especially in those with pre-eclampsia. In contrast to studies showing women with pre-eclampsia to be twice as likely to be nulliparous as women without pre-eclampsia,[23] the authors were unable to demonstrate that gravidity had a significant correlation to diabetes or pre-eclampsia status. These differing results may be attributed to a relatively small sample size of women in some groups as well as a smaller number of pregnant women with pre-existing diabetes or concurrent pre-eclampsia and DM delivering within the Baylor Scott & White hospital system.

Interestingly, though this study found that patients with pre-eclampsia delivered earlier in pregnancy, the women with pre-existing diabetes delivered even earlier than those in the other two pre-eclampsia groups, which suggests the presence of a more severe condition. Several mechanisms have been proposed to explain how hyperglycemia could create an unfavorable placental environment that contributes to the development of pre-eclampsia. Invasive and proliferative abilities of the young cytotrophoblast (CTB) cells are impaired by hyperglycemia during the first trimester of pregnancy. The invasive properties of the CTB cells are essential for creating optimal blood flow to the placenta, and disrupted invasion alters arterial remodeling needed in creating this optimal blood flow.[23] Excess glucose during pregnancy impedes the function of CTB cells by inducing stress and apoptotic signaling pathways; the excess glucose thereafter inhibits MMP-9, which impairs migration and invasion of CTB cells, causing oxidative stress. This oxidative stress leads to placental hypoxia and elevation of interleukin 6, which leads to angiogenic imbalance.[23–25] This series of changes appears to result in a common pathway leading to abnormal placentation and the eventual development of pre-eclampsia.[24] Pre-existing diabetes induces demonstrable alterations in first trimester placental development with significantly reduced placental vascularization indices.[26] Altered carbohydrate metabolism as a result of gestational diabetes causes vascular changes such as arteriosclerosis and a glomerular filtration dysfunction, which can result in a predisposition for pre-eclampsia.[15]

Starikov and colleagues have shown that both type 1 DM and type 2 DM can influence the growth of the placenta. Their study demonstrated that both groups exhibited significantly increased rates in decidual vasculopathy and delayed villous maturity. These pathological changes were related to the uteroplacental (maternal) and placental developmental disorders evident in diabetics compared with the general gravid population. Despite their type 2 DM group having better glycemic control in early pregnancy, they have shown increased uteroplacental circulatory pathology, more placentas with insufficiency and more villous abnormalities were present in type 2 DM placentas compared with the type 1 DM placentas.[1]

Diabetes leads to larger babies at delivery than in normal pregnancies while pre-eclampsia reduced birth size for those with pre-existing diabetes. However, gestational diabetes did not contribute to intrauterine growth restriction in those pregnancies with pre-eclampsia. This supports the concept that altered placental development in the first trimester occurs due to elevated glucose, which may ultimately lead to intrauterine growth restriction later in pregnancy when a second hit triggers pre-eclampsia. Although babies of patients with pre-existing DM who developed pre-eclampsia were not small for gestational age, they were smaller than those from mothers with only prior DM. This suggests that pre-eclampsia in these pregnancies did lead to growth restriction. On the other hand, this difference was not seen in pregnancies with GDM. This helps in understanding the concept that placental development during the first trimester in pregnancies with elevated glucose may be altered and lead to fetal growth restriction later in pregnancy when a second stimulus triggers pre-eclampsia. The significant barriers for research in this population group are limited to the number of pregnant women with

pre-existing diabetes and the difficulties associated with diagnosing pre-eclampsia in women with proteinuria prior to pregnancy.

## CONCLUSION

The current study demonstrates that pre-existing diabetes plays a significant role in placental growth and development during pregnancy. As pregnant women with pre-existing diabetes go on to develop pre-eclampsia, the gestational age at delivery and size of the baby at birth are affected. More studies focus on GDM in pregnancy. Additionally, morphologic and functional studies of the placenta in diabetic mothers have mainly focused on GDM, and most have been carried out in animal models or laboratory cell cultures. It is evident that more research needs to be done to better understand the impact pre-existing diabetes has on placental development and its potential influence on pre-eclampsia. These findings could help guide the design of a prospective study that could further examine the impact of pre-existing DM on placental development in the first trimester and how it may lead to greater susceptibility to restriction when a second stimulus triggers pre-eclampsia later in gestation.

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