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Type 1, Type 2 and Gestational Diabetes Mellitus Differentially Impact Placental Pathologic Characteristics of Uteroplacental Malperfusion

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Abstract

Introduction—During a pregnancy complicated by diabetes, the placenta undergoes a number of functional and structural pathologic changes. However, differences across studies may reflect pathophysiologic differences of diabetes types under investigation.

Methods—We examined placental pathology from women ages 18–40 years with self-identified race/ethnicity; singleton, live births; and type 1 (T1DM; n=36), type 2 (T2DM; n=37), or gestational diabetes mellitus (GDM; n=126). Clinical data were abstracted from medical records. Placental diagnoses were independently re-reviewed by a perinatal pathologist. Multivariable analyses adjusting for race, gestational weight gain, gestational age, and systolic blood pressure were conducted.

Results—Women with T1DM compared with either T2DM or GDM had higher gestational weight gain (mean $\pm$ SD, T1DM vs. T2DM: 28.5 ± 12.4 vs. 20.5 ± 13.4 kg, $p=0.03$; or GDM: 21.3 ± 12.7 kg, $p=0.009$) and insulin use (T2DM: 100.0% vs. 85.3%, $p=0.02$; or GDM: 4.0%, $p<0.001$). Women with T1DM compared with either T2DM or GDM also had a similarly lower prevalence of placental infarcts in univariate analyses; however, these findings did not remain significant after multivariable adjustment. Also, placentas from women with T2DM compared to

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GDM had higher rates of decidual vasculopathy when excluding women with preeclampsia (10.3 vs. 1.6%, $p=0.049$) and diffuse chorangiosis (62.2 vs. 32.5%, $p<0.001$) but a lower rate of villous immaturity (10.8 vs. 90.5%, $p=0.007$) after full adjustment.

Discussion—Placental vasculopathic abnormalities differ by maternal diabetes type, potentially reflecting underlying pathophysiologic mechanisms. Further research on placental pathology and metabolic derangements is warranted.

Keywords

placental pathology; vasculopathy; gestational diabetes mellitus; type 1 diabetes mellitus; type 2 diabetes mellitus

Introduction

The placental vasculature is composed of both maternal and fetal compartments which are physically isolated and separated by a trophoblastic shell (1). Nonetheless, the maternal-placental and fetal-placental circulations exchange blood at the terminal villi. Maternal complications of pregnancy, such as maternal diabetes (2), and fetal morbidities, including stillbirth (3) and fetal growth abnormalities (3, 4), have been significantly associated with placental vascular abnormalities. However, the association of placental vascular abnormalities with various diabetes types has not been well elucidated; therefore, an enhanced understanding of the effect of maternal diabetes on placental pathology and, specifically, placental vasculature is warranted.

Derangements in maternal-placental, also known as uteroplacental, circulation are evidenced in placental pathology by placental infarction, abruption, or villous developmental changes resulting from abnormal uteroplacental blood flow (5, 6). These pathologies comprise uteroplacental malperfusion or underperfusion (7) and have been described in relation to maternal diabetes (2). Abnormalities in fetal-placental circulation are evidenced by fetal vascular lesions, including chorangiosis and fetal thrombotic vasculopathy (5). Because maternal disorders may induce placental vascular changes in the uteroplacental and fetal-placental circulations (3), we aimed to identify placental pathologic characteristics representing both vascular compartments.

Placentas from pregnancies affected by pregestational diabetes mellitus, that is type 1 (T1DM) or type 2 (T2DM), are potentially exposed to a hyperglycemic milieu early in placental development, whereas placentas from pregnancies affected by gestational diabetes mellitus (GDM) may only be exposed to significant hyperglycemia in the late second or early third trimester of pregnancy as placental mass increases (8). This difference in the duration of hyperglycemia exposure may manifest as placental vasculature pathology. Moreover, differences in placental pathology based on diabetes type may elucidate mechanisms underlying these pathologic changes. Consequently, we sought to compare placental pathology from pregnancies complicated by T1DM, T2DM, or GDM in order to characterize pathologic differences across diabetes types in a well-defined population and to generate hypotheses regarding potential etiologic mechanisms underlying these differences. We hypothesized that placentas from women with pregestational diabetes would reflect

more placental pathology due to presumed earlier exposure to hyperglycemia than placentas from women with GDM.

Methods

Population Selection

Women with pregestational diabetes were selected from placental pathology specimens received in the Massachusetts General Hospital (MGH) Department of Pathology between January 1, 2001 and December 31, 2009 using the terms "diabetes," "IDDM," "DM", "GDM", and "glucose." Women with singleton pregnancies and complete placental data were identified with diagnoses confirmed by chart review of medical history, medication prescriptions, and laboratory data including antibody and C-peptide levels (n=98). We refined the population described by Beauharnais et al. (9) to include only the first pregnancy for women who delivered singleton live births diagnosed with T1DM (n=36) or T2DM (n=37). Women with pregestational diabetes delivered between 32.3 and 40.9 weeks gestational age.

Women with GDM were identified from among women who presented for prenatal care to the MGH Obstetrical Department between September 1998 and January 2007 (n = 178). We then selected those with biochemically-confirmed GDM (n=157) diagnosed by Carpenter-Coustan criteria on a 100-g oral glucose tolerance test (10). Women who delivered singleton, full-term, live births (n=129) and self-reported race/ethnicity (n=126) were included in the study. We also examined glycemic control by aggregating all women then stratifying by "high" (> 6.0%) and "low" (<= 6.0%) HbA1c. All participants provided informed written consent prior to study participation; the Partners Human Research Committee Institutional Review Board approved the study protocol (11).

Clinical Examination

Standardized medical record review was conducted to obtain maternal age; parity; gravidity; height and weight at first prenatal visit; gestational weight gain, calculated as weight at delivery minus the weight at first prenatal visit; body mass index (BMI) calculated as weight (kilograms) divided by height (meter squared); systolic and diastolic blood pressures (mmHg); gestational age at delivery (weeks); infant birth weight (grams); insulin use; and smoking history. Race/ethnicity was categorized as non-Hispanic white or white. Preeclampsia was defined as normotension (blood pressure, BP < 140/90 mm Hg) at the first prenatal visit (first trimester) followed by hypertension and proteinuria (≥ 0.3 grams protein/24 hours or dipstick 2+ protein) after 20 weeks gestation. Mean hemoglobin A1c (HbA1c) was calculated in each trimester.

Placental Examination

Placentas from women with diabetes routinely receive a full pathologic examination at MGH. A standard gross template was followed (Supplement 1) and the cord, membranes, and parenchymas were sampled for histology. Three sections of the parenchyma were examined. Although the MGH team of perinatal pathologists performed all gross placental examinations and histopathologic readings, DJR re-reviewed all placental pathology for this

study. The gross parameter examined and scored was the trimmed placental weight. Histopathologic parameters diagnosed and scored using standardized and published criteria included villous maturation (12), villous maturational arrest (13), chorangiosis (14), villitis of unknown etiology (15), acute chorioamnionitis classified using the Redline nosology (16), fetal acute chorioamnionitis (17), placental infarct (12), fetal thrombotic vasculopathy (18), and decidual vasculopathy (12).

We aggregated the placental pathologic findings into four broadly-defined categories. The vasculopathic characteristics were divided into maternal and fetal compartments. The maternal vasculopathies included decidual vasculopathy and placental infarct. The fetal vasculopathies included chorangiosis and fetal thrombotic vasculopathy. The third category comprised measures of maturational changes including placental weight, arrested villous maturation, mature, immature, or hypermature. Finally, inflammatory characteristics were acute chorioamnionitis, fetal acute chorioamnionitis, and chronic villitis which includes villitis of unclear or unknown etiology.

Statistical Analysis

The clinical and placental pathologic parameters were compared across the three diabetes types. Continuous variables were summarized using means and standard deviations or medians (quartile 1, quartile 3). Categorical variables were summarized using counts and percentages. Independent sample t tests, Mann-Whitney U tests, or chi-square tests were used for between group comparisons. Multivariable analyses with adjustments for race, gestational weight gain, gestational age, and systolic blood pressure were conducted. P-values less than 0.05 were considered statistically significant. Because we performed a descriptive analysis of observational data, adjustment for multiple testing was not necessary (19). However, in order to address the potential impact of multiple comparisons on statistical significance, the Bonferroni correction was also applied. P-values less than 0.004 were considered significant after Bonferroni correction. The statistical analyses were performed using SAS for Windows, version 9.1 (SAS Institute, Cary, NC).

Results

Clinical Characteristics

Baseline characteristics of the 199 participants are listed in Table 1. Although maternal age and birth weight were similar across diabetes types, women with T2DM (n=37) compared to GDM (n=126) had greater body mass index (35.8 ± 8.7 vs. 30.0 ± 6.7 , $p < 0.001$) and a higher prevalence of preeclampsia (14.3 vs. 1.6%, $p < 0.001$). Women with T1DM (n=36) compared to women with either T2DM or GDM had higher gestational weight gain (T1DM vs. T2DM: 28.5 ± 12.4 vs. 20.5 ± 13.4 kg, $p = 0.03$; or GDM: 21.3 ± 12.7 kg, $p = 0.009$) and insulin use (T1DM vs. T2DM: 100.0 vs. 85.3%, $p = 0.02$; or GDM: 4.0%, $p < 0.001$), but lower frequency of non-white race (T1DM vs. T2DM: 25.0 vs. 67.6%, $p < 0.001$; or GDM: 61.9%, $p < 0.001$). Compared to women with T1DM, women with GDM had lower HbA1c values in the second trimester (5.3 ± 0.8 vs. $6.4 \pm 0.7\%$, $p = 0.03$) and lower 1st trimester systolic blood pressures (112 ± 12 vs. 119 ± 13 mmHg, $p = 0.006$). Additionally, women with GDM compared to women with pregestational diabetes delivered at later gestational ages (GDM vs. T1DM:

39.3 $\pm$ 1.1 vs. 37.5 $\pm$ 2.1 weeks, $p < 0.001$; or T2DM: 38.0 $\pm$ 1.9 weeks, $p < 0.001$) and had lower HbA1c values in the third trimester (GDM vs. T1DM: 5.7 $\pm$ 0.5 vs. 6.4 $\pm$ 0.8%, $p = 0.006$; or T2DM: 6.4 $\pm$ 0.9%, $p = 0.04$). When comparing “low” vs. “high” HbA1c, placental infarcts were more prevalent (25.0 vs. 5.0%; $p = 0.04$) and villous maturity was less prevalent (41.7 vs. 69.7%; $p = 0.03$; Supplement 2, including preeclampsia). Only placental infarcts differed after excluding preeclampsia (Supplement 3). Notably, there was no statistically significant difference in tobacco use across the three groups.

Placental Pathologic Characteristics

Maternal vasculopathic changes significantly differed among the three diabetes types (Table 2). In univariate analyses, placentas from pregnancies complicated by T1DM compared to T2DM or GDM had a lower prevalence of placental infarcts (T1DM vs. T2DM: 2.8 vs. 24.3%, $p = 0.007$; or GDM: 15.9%, $p = 0.04$). Placentas from women with T2DM compared to GDM or T1DM had greater rates of decidual vasculopathy, but statistical significance was achieved only when comparing against GDM (8.3 vs. 1.6%, $p = 0.04$). Moreover, these findings did not remain significant after adjusting for race, gestational weight gain, gestational age, and systolic blood pressure. Notably, when excluding women with preeclampsia ($n = 18$; Table 3), women with T2DM compared to GDM had greater rates of decidual vasculopathy after multivariable adjustment (10.3 vs. 1.6%, $p = 0.049$).

When considering fetal vasculopathic changes, there were no statistically significant differences in fetal thrombotic vasculopathy across the three diabetes types (Table 2). After full adjustment, chorangiosis was present more commonly among the women with pregestational compared to gestational diabetes, notably among those with diffuse chorangiosis (GDM vs. T1DM: 32.5 vs. 55.6%, $p = 0.01$; or T2DM: 62.2%, $p < 0.001$).

Regarding maturational changes, there were no statistically significant differences in maturation arrest but placentas from women with GDM had significantly more villous immaturity compared to those with pregestational diabetes (GDM vs. T1DM: 90.5 vs. 27.8%, $p = 0.02$; or T2DM: 10.8%, $p = 0.007$) after full multivariable adjustment (Table 2). The difference between T1DM and T2DM in villous immaturity was not statistically significant ($p = 0.89$). Consequently, women with GDM compared to women with pregestational diabetes had lower rates of villous maturity (GDM vs. T1DM: 7.1 vs. 52.8%, $p < 0.001$; or T2DM: 75.7%, $p < 0.001$). When examining inflammatory changes, there were no differences across the three groups in maternal acute chorioamnionitis or villitis of unclear or unknown origin (Table 2). However, placentas from pregnancies complicated by GDM compared to T2DM had a ten-fold lower rate of fetal acute chorioamnionitis (1.6 vs. 11.1 %; $p = 0.008$) in univariate analysis; this difference did not achieve statistical significance in the fully-adjusted model ($p = 0.08$). After excluding women with preeclampsia, these findings were similar except villous immaturity was no longer significantly different between women with GDM and T1DM (Table 3).

Discussion

We analyzed the placental pathology of 199 women with T1DM, T2DM, or GDM who delivered at a single hospital and we observed several differences in placental pathology

according to diabetes type. We found that women with T2DM or GDM shared placental pathologic features related to uteroplacental malperfusion. Uteroplacental malperfusion is thought to be due to decreased or abnormal uterine artery blood flow and has been associated with intrauterine fetal growth restriction and fetal death (5). Pathologic features consistent with uteroplacental malperfusion include placental infarcts, accelerated villous maturation, and an increase in maternal vascular lesions such as decidual vasculopathy (7, 20, 21). In order to examine the impact of diabetes on the placental vasculature, we examined several aspects of placental vasculopathy across the maternal and fetal compartments.

In our study, placentas from pregnancies complicated by T2DM or GDM were observed to have a greater incidence of maternal vasculopathy compared to placentas from pregnancies complicated by T1DM. We observed that placentas from pregnancies complicated by T2DM compared to GDM had a significantly greater incidence of decidual vasculopathy, even after excluding women with preeclampsia. Additionally, women with T2DM or GDM were more likely to have placental infarcts than women with T1DM in univariate analyses. Although our sample size may have limited our ability to detect additional differences, Starikov et al. (2) also proposed that uteroplacental malperfusion occurred at higher rates in placentas of women with T2DM compared to T1DM as measured by decidual vasculopathy. Notably, they did not find a difference in placental infarct prevalence between groups. Because GDM shares several pathophysiologic characteristics with T2DM, including insulin resistance, impaired insulin secretion (22), and increased risk of subsequent T2DM and CVD (8, 23), similarities in placental pathology indicative of uteroplacental malperfusion may reflect similarities in pathophysiology between GDM and T2DM.

Moreover, we observed that fetal vasculopathic changes occurred more commonly among pregnancies complicated by pregestational rather than gestational diabetes. Women with T1DM or T2DM had significantly higher rates of chorangiosis, specifically diffuse chorangiosis, compared to those with GDM. Although smoking has been associated with chorangiosis (24, 25), we did not observe a significant difference in smoking history among these three groups. Notably, prior studies have reported chorangiosis in women with GDM (25–27) and we observed a moderate prevalence among the women with GDM in this study, albeit less than the prevalence observed among the women with pregestational diabetes. Nevertheless, although these findings are provocative, confirmation in a larger population study may serve to provide insight into etiologic mechanisms for these relationships.

Regarding maturational changes, we observed that women with gestational compared to pregestational diabetes had significantly greater rates of villous immaturity, a placental abnormality that has been independently associated with an increased risk of perinatal mortality (28). Because defects in placental maturation have been associated with chronic fetal hypoxia (13, 29), a greater rate of villous immaturity may be indicative of a greater pre-uterine hypoxic environment. Prior studies have observed an increased incidence of placental villous immaturity in placentas affected by either pregestational diabetes (30–32) or GDM (26, 27) compared to normoglycemic pregnancies. In contrast to our study, Dubova et al. found villous immaturity to be more common in T1DM compared to GDM, albeit in a population with a significantly smaller sample size (33). Nonetheless, these studies suggest

that metabolic abnormalities such as diabetes may impact placental development as evidenced by villous immaturity.

Regarding inflammatory changes, we observed that placentas from women with T2DM compared to GDM have a greater incidence of fetal acute chorioamnionitis. Because chorioamnionitis has been associated with preterm births and preterm premature rupture of membranes (34, 35), this finding may be due to the earlier gestational age at delivery of women with T2DM versus GDM in our study. However, further study in larger populations of women with maternal diabetes mellitus is necessary to clarify these relationships.

In order to elucidate the mechanisms underlying these observed pathologic findings, we considered the impact of clinical factors such as insulin use and glycemic control; and pregnancy complications such as preterm birth and preeclampsia. Compared to women with GDM, women with T1DM had significantly higher insulin use and less well-controlled glycemia, characterized by higher second and third trimester HbA1c values. These differences might also reflect the earlier onset and longer duration of diabetes in pregnancies of women with pregestational diabetes compared to those with GDM. Additionally, because the metabolic derangements in GDM occur in the latter stages of pregnancy (36), GDM is generally responsible for fewer birth defects than observed in pregestational diabetes (37).

We also observed that women with pregestational diabetes delivered at earlier gestational ages than those with GDM. Earlier gestational ages have previously been associated with greater incidence of placental lesions in women with preeclampsia (38). However, our findings remained significant after controlling for preeclampsia, suggesting that these changes were independent of preeclampsia. In fact, the only differences we observed in our results with and without the women with preeclampsia were the loss of significance in chorangiosis rates between women with GDM and T1DM and gain of significance when comparing villous immaturity between women with T1DM to T2DM (Table 3). Nevertheless, because placental vascular lesions have been associated with adverse maternal (39) and fetal outcomes (5), further examinations of the impact of clinical factors on the incidence of vasculopathic changes in women with pregestational diabetes or GDM are warranted.

Strengths of our study include the histological confirmation of placental diagnoses and the biochemical confirmation of GDM diagnoses. Furthermore, by only including women with singleton, live births and controlling for preeclampsia through additional analyses, there is a reduced possibility that observed differences may be due to concomitant pregnancy complications. One limitation of this study is the smaller sample size of women diagnosed with T1DM or T2DM relative to the number of women with GDM, potentially limiting our ability to observe differences.

To our knowledge, this is the first study simultaneously comparing placental pathology among women with T1DM, T2DM, or GDM (40). Our results revealed a comparable degree of uteroplacental malperfusion reflected by decidual vasculopathy in placentas of women with T2DM or GDM. Women with pregestational diabetes were also associated with more derangements in the fetal vasculature than those with GDM. These data patterns could

suggest that the pathophysiology associated with type of diabetes, such as insulin resistance commonly found in pregnancies complicated by GDM or T2DM, influenced the placental pathology. However, future studies of placental pathology are required in order to elucidate mechanistic similarities and differences across these three types of maternal diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

GDM	gestational diabetes mellitus
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
MGH	Massachusetts General Hospital

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Highlights

- Type 1, type 2 and gestational diabetes differentially impact placental pathology
- Type 2 and gestational diabetes have more maternal vasculopathic changes
- Pregestational diabetes is associated with more fetal vasculopathic changes
- Gestational diabetes is associated with a greater rate of villous immaturity
- Diabetes may adversely impact the placenta despite good glycemic control

Table 1**Baseline Clinical Characteristics by Diabetes Type**

	GDM (n=126)	T1DM (n=36)	T2DM (n=37)	P-value (GDM vs. T1DM)	P-value (GDM vs. T2DM)	P-value (T2DM vs. T1DM)
Age (years)	32.2 ± 5.7	32.2 ± 6.1	32.1 ± 5.6	0.99	0.88	0.92
Non-white race (%)	78 (61.9)	9 (25.0)	25 (67.6)	<0.001*	0.53	<0.001*
Body mass index (kg/m ²)	30.0 ± 6.7	31.6 ± 7.2	35.8 ± 8.7	0.32	<0.001*	0.08
Parity	1 (0, 1)	2 (1, 2)	2 (1, 4)	<0.001*	<0.001*	0.27
Gravidity	2 (1, 4)	2 (1, 2)	2 (1, 4)	0.06	0.86	0.27
Systolic blood pressure (mmHg)	112 ± 12	119 ± 13	113 ± 12	0.006*	0.61	0.08
Diastolic blood pressure (mmHg)	69 ± 8	72 ± 10	71 ± 10	0.12	0.31	0.71
Gestational age (weeks)	39.4 ± 1.1	37.5 ± 2.1	38.0 ± 1.9	<0.001*	<0.001*	0.34
Gestational weight gain (kg)	21.3 ± 12.7	28.5 ± 12.4	20.5 ± 13.4	0.009*	0.77	0.03*
Birth Weight (grams)	3669 ± 625	3420 ± 877	3458 ± 685	0.06	0.08	0.84
Birth Weight for Gestational Age (Percentile)	62.6 ± 30.1	62.9 ± 32.7	62.4 ± 33.5	0.95	0.97	0.94
Preeclampsia (%)	2 (1.6)	8 (22.9)	5 (14.3)	<0.001*	0.001*	0.36
Active smoker (%)	8 (12.7)	2 (5.9)	5 (15.6)	0.29	0.69	0.20
1 st trimester HbA1c (%)	---	7.4 ± 1.5	7.4 ± 1.6	---	---	0.85
2 nd trimester HbA1c (%)	5.3 ± 0.8	6.4 ± 0.8	6.3 ± 0.9	0.03*	0.07	0.67
3 rd trimester HbA1c (%)	5.7 ± 0.5	6.4 ± 0.8	6.4 ± 0.9	0.006*	0.04*	0.73
Insulin use (%)	5 (4.0)	35 (100.0)	29 (85.3)	<0.001*	<0.001*	0.02*

Table shows number (percentage), mean ± standard deviation, or median (quartile 1, quartile 3)

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; GDM = gestational diabetes mellitus

* Significant at P<0.05

Table 2

Placental Pathology by Diabetes Type, including Women with Preeclampsia

	Univariate					Multivariable ^{††}				
	GDM (n=126)	T1DM (n=36)	T2DM (n=37)	P-value (GDM vs. T1DM)	P-value (GDM vs. T2DM)	P-value (T2DM vs. T1DM)	P-value (GDM vs. T1DM)	P-value (GDM vs. T2DM)	P-value (T2DM vs. T1DM)	
Maternal vasculopathy										
Decidual vasculopathy (%)	2 (1.6)	1 (2.8)	3 (8.3)	0.64	0.04 [*]	0.30	0.46	0.07	0.93	
Placental infarct (%)	20 (15.9)	1 (2.8)	9 (24.3)	0.04 [*]	0.24	0.007 [*]	n/a	0.83	n/a	
Fetal vasculopathy										
Chorangioma (%)	48 (38.1)	23 (63.9)	28 (77.8)	0.006 [*]	<0.001 ^{††}	0.19	0.01 [*]	<0.001 ^{††}	0.94	
Chorangioma, focal (%)	7 (5.6)	3 (8.3)	5 (13.5)	0.54	0.10	0.48	0.93	0.66	0.08	
Chorangioma, diffuse (%)	41 (32.5)	20 (55.6)	23 (62.2)	0.01 [*]	0.001 ^{††}	0.57	0.01 [*]	<0.001 ^{††}	0.34	
Fetal thrombotic vasculopathy (%)	9 (7.2)	4 (11.1)	4 (10.8)	0.45	0.48	0.97	0.25	0.20	0.25	
Maturation Characteristics										
Placental weight (g)	535.7 ± 133.3	492.14 ± 150.9	488.56 ± 124.1	0.10	0.06	0.91	0.55	0.37	0.87	
Villous maturational arrest (%)	0 (0.0)	1 (2.8)	0 (0.0)	0.06	n/a	0.31	n/a	n/a	n/a	
Villous maturity (%)	9 (7.1)	19 (52.8)	28 (75.7)	<0.001 ^{††}	<0.001 ^{††}	0.04 [*]	<0.001 ^{††}	<0.001 ^{††}	0.89	
Villous immaturity (%)	114 (90.5)	10 (27.8)	4 (10.8)	<0.001 ^{††}	<0.001 ^{††}	0.07	0.02 [*]	0.007 [*]	0.89	
Villous hypermaturity (%)	3 (2.4)	4 (11.1)	4 (10.8)	0.02 [*]	0.03 [*]	0.97	0.75	0.18	0.14	
Inflammatory Characteristics										
Acute chorioamnionitis (%)	22 (17.5)	4 (11.1)	6 (16.7)	0.36	0.91	0.50	0.76	0.67	0.33	
Fetal acute chorioamnionitis (%)	2 (1.6)	1 (2.8)	4 (11.1)	0.64	0.008 [*]	0.16	0.50	0.08	0.62	
Villitis of unclear etiology (%)	26 (20.6)	3 (8.3)	7 (18.9)	0.09	0.82	0.19	0.56	0.37	0.61	

Table shows number (percentage) or mean ± standard deviation

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; GDM = gestational diabetes mellitus

^{††} Adjusted for race, gestational weight gain, gestational age, and systolic blood pressure^{*} Significant at P<0.05 (Unadjusted)[†] Significant at P<0.004 (Bonferroni correction)

Table 3

Placental Pathology by Diabetes Type, excluding Women with Preeclampsia[†]

	Univariate				Multivariable ^{††}				
	GDM (n=124)	T1DM (n=27)	T2DM (n=30)	P-value (GDM vs. T1DM)	P-value (GDM vs. T2DM)	P-value (T2DM vs. T1DM)	P-value (GDM vs. T1DM)	P-value (GDM vs. T2DM)	P-value (T2DM vs. T1DM)
Maternal vasculopathy									
Decidual vasculopathy (%)	2 (1.6)	1 (3.7)	3 (10.3)	0.48	0.02*	0.33	0.24	0.049*	0.87
Placental infarct (%)	20 (16.1)	0 (0.0)	7 (23.3)	0.03*	0.35	0.007*	n/a	0.94	n/a
Fetal vasculopathy									
Chorangiosis (%)	48 (38.7)	16 (59.3)	22 (75.9)	0.05	<0.001**	0.18	0.04*	0.002**	0.75
Chorangiosis, focal (%)	7 (5.7)	0 (0.0)	4 (13.3)	0.21	0.14	0.049*	n/a	n/a	n/a
Chorangiosis, diffuse (%)	41 (33.1)	16 (59.3)	18 (60.0)	0.01*	0.007*	0.95	0.01*	<0.001**	0.75
Fetal thrombotic vasculopathy (%)	9 (7.3)	2 (7.4)	4 (13.3)	0.99	0.29	0.47	0.16	0.12	0.26
Maturation Characteristics									
Placental weight (g)	537.4 ± 134.2	499.6 ± 162.6	506.8 ± 117.5	0.21	0.30	0.85	0.91	0.68	0.43
Villous maturational arrest (%)	0 (0.0)	0 (0.0)	0 (0.0)	n/a	n/a	n/a	n/a	n/a	n/a
Villous maturity (%)	9 (7.3)	15 (55.6)	23 (76.7)	<0.001**	<0.001**	0.09	<0.001**	<0.001**	0.61
Villous immaturity (%)	112 (90.3)	8 (29.6)	2 (6.7)	<0.001**	<0.001**	0.02*	0.09	0.03*	0.61
Villous hypermaturity (%)	3 (2.4)	3 (11.1)	4 (13.3)	0.04*	0.01*	0.80	n/a	0.13	n/a
Inflammatory Characteristics									
Acute chorioamnitis (%)	21 (16.9)	4 (14.8)	5 (17.2)	0.79	0.97	0.80	0.41	0.82	0.18
Fetal acute chorioamnionitis (%)	2 (1.6)	1 (3.7)	3 (10.3)	0.48	0.02*	0.33	0.31	0.31	0.45

Table shows number (percentage) or mean ± standard deviation

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; GDM = gestational diabetes mellitus

^{††} Adjusted for race, gestational weight gain, gestational age, and systolic blood pressure

* Significant at P<0.05

[‡] Significant at P<0.004 (Bonferroni correction)

Note: Preeclampsia status could not be determined for n=1 T1DM and n=2 T2DM; therefore, these women were excluded from data in Table 3

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