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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 ± 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 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.

1. 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-

Abbreviations: GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; MGH, Massachusetts General Hospital.

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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.

2. Methods

2.1. 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].

2.2. 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 g protein/24 h or dipstick 2 + protein) after 20 weeks gestation. Mean hemoglobin A1c (HbA1c) was calculated in each trimester.

2.3. 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.

2.4. 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).

3. Results

3.1. 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