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Placental maternal vascular malperfusion and adverse pregnancy outcomes in gestational diabetes mellitus

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ABSTRACT

Introduction: Maternal vascular malperfusion (MVM) lesions represent hypoxic-ischemic damage to the placenta, and they are associated with adverse pregnancy outcomes. Women with gestational diabetes (GDM) are at increased risk for pregnancy complications, so we set out to characterize the prevalence and clinical correlates of MVM lesions in this cohort.

Methods: This was a retrospective cohort study of 1187/1374 (86.4%) women with GDM delivered between 2009 and 2012 who had placental pathology available. Placental lesions of all types were tabulated and grouped into constructs of related entities. MVM lesions specifically included villous infarcts, decidual vasculopathy, increased syncytial knots, perivillous fibrin, and fibrin deposition. We compared maternal characteristics between women with and without MVM lesions, and we also assessed the impact of these lesions on birth weight, preterm birth, and pre-eclampsia using multivariable logistic regression analysis.

Results: MVM lesions were the most common placental lesion type in women with GDM (n = 362, 30.5%). Excess gestational weight gain was independently associated with MVM lesions (aOR 1.42, 95% CI 1.06–1.91, p = 0.02) after adjusting for maternal characteristics. MVM lesions were associated with lower birth weight (−90.3 g, 95% CI -148.0 to −32.7, p = 0.002), as well as a 2-fold increased risk for delivery of a small for gestational age infant (10.8 vs 5.9%, p = 0.01) in overweight and obese women. MVM lesions were also associated with increased risk for preterm birth <34 weeks (adjusted OR 2.36, 95% CI 1.31–4.23, p = 0.004) and hypertensive disorders of pregnancy (HDP; adjusted OR 1.58, 95% CI 1.13–2.22, p = 0.02).

Discussion: Placental maternal vascular malperfusion lesions may be one pathway linking excess gestational weight gain to adverse pregnancy outcomes in women with GDM, and future studies are needed to identify metabolic factors that may explain this association.

1. Introduction

Gestational diabetes mellitus (GDM) affects approximately 7% of pregnancies [1], and it can result in adverse pregnancy outcomes including fetal overgrowth [2] and pre-eclampsia [2,3]. In addition to dysglycemia, gestational diabetes is associated with obesity and excess gestational weight gain [4], both of which also increase the risk for pregnancy complications. Although GDM is commonly diagnosed in the late second and early third trimester, metabolic perturbations including increased triglycerides [5] and alterations in various inflammatory cytokines and adipokines may occur much earlier in gestation [6].

Less is known about the relationship between placental

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pathology lesions and adverse pregnancy outcomes in women with GDM. The placenta reflects the metabolic milleu of both the mother and fetus and it can shed light on the metabolic alterations that occur during pregnancy. Oxygenated maternal blood flows through remodeled spiral arteries that traverse the maternal myometrium and decidua before emptying into the placental intervillous space. A trophoblast layer separates this maternal compartment of the placenta from the fetal vessels of the placental vasculature. The maternal and placental circulations then exchange oxygen and nutrients across this trophoblast barrier at the level of the terminal villus. Consequently, placental dysfunction can lead to a number of adverse pregnancy and neonatal outcomes [7,8].

Placental MVM lesions develop as a consequence of deficient trophoblastic invasion and remodeling of the spiral arterioles in early pregnancy [9], and these lesions are a common pathologic finding that may contribute to or represent damage from placental hypoxia [10]. Maternal malperfusion is of clinical significance, because many aspects of this entity have been associated with severe pregnancy-related complications [11]. Many MVM lesions were originally described in the context of pre-eclampsia, and these lesions were considered relatively specific for pre-eclampsia. However, it is now known that these lesions can be found in systemic lupus erythematosus, antiphospholipid antibody syndrome, fetal growth restriction, preterm labor, preterm premature rupture of membranes, placental abruption, and stillbirth [11], but the maternal characteristics that are associated with the development of these lesions are incompletely understood. Because women with GDM are at increased risk for adverse outcomes, the goal of this analysis was to characterize the prevalence of placental lesions in women with GDM with a focus on maternal factors associated with MVM lesions. We also sought to assess the impact of placental MVM lesions on birth weight, preterm birth, and hypertensive disorders of pregnancy in women with GDM.

2. Methods

This was a retrospective cohort study that included women with singleton gestations and GDM who were delivered at Magee-Womens Hospital (University of Pittsburgh, Pittsburgh, PA) from January 2009 to October 2012 were included. Details of the cohort derivation were presented previously [4], but in brief we identified 1374 women who were diagnosed with GDM using either a 50 g, 1 h glucose challenge test (GCT) that exceeded 200 mg/dL, or if they had two or more abnormal values on a 3 h, 100 g oral glucose tolerance test (OGTT) as defined by the Carpenter-Coustan Criteria [12]. Medical records were reviewed to confirm all diabetes diagnoses, and women who reported a diagnosis of diabetes at their first prenatal visit or those with a first trimester HbA1c value > 6.5% were considered to have pre-gestational diabetes and excluded. Placentas from women with GDM were routinely sent for pathologic evaluation, and we included 1186/1374 (86.3%) of women with GDM who had placental pathology available.

Placental pathology data were matched to patients with GDM using the Magee Obstetric Medical and Infant (MOMI) database. All placentas were examined for clinical indications, therefore a limited amount of clinical history was available to the pathologist. Our placenta pathology matching and extraction process has been described previously. Briefly, placental pathology reports were reformatted into Extensible Markup Language (XML) using Java and then A SQL Server Integration Services package (SSIS) extracted and transformed this text information into SQL Server tables that were then linked to the MOMI database. With the assistance of a placental pathologist (WTP), lesions were then grouped into categories including maternal vascular malperfusion (MVM; decidual vasculopathy, villous infarction, advanced villous maturation, increased perivillous fibrin deposition, increased intervillous fibrin deposition), ascending intrauterine infection (AIUI; acute chorioamnionitis, acute funisitis, acute vasculitis, acute deciduitis), villitis of unknown etiology (VUE; a chronic inflammatory infiltrate in the villi), fetal thrombosis, or chorangiosis (Supplemental Table 1 contains definitions used for each lesion type) [13–15]. Because lesions associated with ascending infection were unlikely to be specifically related to gestational diabetes, these lesions were excluded from further analysis. A validation study demonstrated excellent sensitivity and specificity for MVM lesions when automated abstraction was compared to manual record abstraction [13]. In addition, a number of cases (n = 56 spontaneous PTBs, 19 medically indicated PTBs, and 50 term births) were reviewed by a single pathologist blinded to all clinical information except gestational age (WTP). MVM lesions demonstrated good agreement (62%) in preterm birth and excellent agreement among term births (82%).

To assess maternal glycemic control, 7 days of consecutive blood glucose values were obtained from the medical record at 4 week intervals. Blood glucose data were available for 989/1186 women (83.4%), and the mean fasting and postprandial blood glucose values were calculated across gestation. Decisions regarding initiation of glyburide or insulin were made by the treating physician, and both dose at initiation of therapy and dose at delivery were abstracted from the medical record. Pre-pregnancy BMI was calculated using the patient-reported pre-pregnancy weight, and gestational weight gain was categorized as insufficient, sufficient, or excessive as defined in the Institute of Medicine 2009 guidelines [16]. In women with preterm delivery (n = 186) we estimated the maximal recommended weight gain at the gestational age at which they were delivered by multiplying the maximal weekly weight gain in the second and third trimesters times the number of weeks preterm the patient was delivered and subtracting this value from the maximum recommended weight gain for each BMI category [17].

The primary objectives of our study were to establish maternal factors related to MVM lesions and to assess the relationship between these lesions and pregnancy outcomes. Our primary pregnancy outcomes included birth weight, preterm birth, and hypertensive disorders of pregnancy. Birth weight categories including large for gestational age (>90th percentile for gestational age) or small for gestational age (<10th percentile for gestational age) birth weight status based on US national birth weight data [18] were compared between women with and without MVM lesions. We also calculated the birthweight z-scores using population-based birthweight data from our hospital over a 3 year period. Preterm births (<37 or <34 weeks) were further characterized as spontaneous (following the spontaneous onset of contractions or premature rupture of membranes) or indicated preterm birth, which encompassed all other preterm deliveries. Hypertensive disorders of pregnancy were considered together as a single outcome, and they were also individually defined as follows: gestational hypertension consisted of blood pressures ≥140/90 mmHg on two or more occasions 6 h apart after 20 weeks gestation without proteinuria, while pre-eclampsia without severe features was defined as the same blood pressure threshold accompanied by detectable urinary protein (urinary protein: creatinine ratio >0.3 or ≥ 0.3 g/24 h). Criteria for preeclampsia with severe features included blood pressures ≥160/110 mmHg, Eclampsia, pulmonary edema, oliguria (<500 ml/24 h), fetal growth restriction, or symptoms suggestive of significant end-organ involvement (headache, visual disturbance, or epigastric or right upper quadrant pain). Superimposed pre-eclampsia was diagnosed in women with chronic hypertension who had blood pressure exacerbations along with new-onset proteinuria (≥0.3 g/24 h).