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Maternal obesity and sex-specific differences in placental pathology

Sandra M. Leon-Garcia [a], Hilary A. Roeder [a], Katharine K. Nelson [b], Xiaoyan Liao [b], Donald P. Pizzo [b], Louise C. Laurent [a], Mana M. Parast [b], D. Yvette LaCoursiere [a, *]

[a] Department of Reproductive Medicine, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA
[b] Department of Pathology, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA

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ABSTRACT

Objective: Adverse effects of obesity have been linked to inflammation in various tissues, but studies on placental inflammation and obesity have demonstrated conflicting findings. We sought to investigate the influence of pregravid obesity and fetal sex on placental histopathology while controlling for diabetes and hypertension.

Methods: Placental histopathology focusing on inflammatory markers of a cohort of normal weight (BMI = 20–24.9) and obese (BMI ≥ 30) patients was characterized. Demographic, obstetric and neonatal variables were assessed.

Results: 192 normal and 231 obese women were included. Placental characteristics associated with obesity and fetal sex independent of diabetes and hypertension were placental disc weight >90th percentile, decreased placental efficiency, chronic villitis (CV), fetal thrombosis, and normoblastemia. Additionally, female fetuses of obese mothers had higher rates of CV and fetal thrombosis. Increasing BMI increased the risk of normoblastemia and CV. The final grade and extent of CV was significantly associated with obesity and BMI, but not fetal gender. Finally, CV was less common in large-for-gestation placentas.

Conclusions: Maternal obesity results in placental overgrowth and fetal hypoxia as manifested by normoblastemia; it is also associated with an increased incidence of CV and fetal thrombosis, both more prevalent in female placentas. We have shown for the first time that the effect of maternal obesity on placental inflammation is independent of diabetes and hypertension, but significantly affected by fetal sex. Our data also point to the intriguing possibility that CV serves to normalize placental size, and potentially fetal growth, in the setting of maternal obesity.

1. Introduction

Over the last decade, studies have established that maternal obesity increases morbidity and mortality for the maternal–fetal dyad [1,2]. Maternal morbidities include gestational diabetes mellitus (GDM), gestational hypertension (GHTN), preeclampsia/eclampsia [1,3], labor dystocia [4], operative and Cesarean delivery, and postpartum hemorrhage [5]. Offspring of obese mothers are at a higher risk of macrosomia (birth weight > 4 kg) as well as intrauterine fetal demise (IUFD) [6,7]. Furthermore, these neonates are at increased risk of obesity and metabolic disease later in their own adult life [8,9].

Several studies support the association between pregravid obesity and placental pathology. These include an association with increased placental weight and reduced efficiency, the latter measured as a ratio of birthweight to placental weight [10,11]. Likewise, inflammation in the form of chorioamnionitis has been documented in placentas of obese women [11,12]; this lesion is most often a mixed infiltrate composed of neutrophils and lymphocytes and is thought to be maternal in origin, although it can be accompanied by a fetal response [13]. This is not surprising given the increased risk of labor dystocia and prolonged ruptured membranes [4].

However, the more common inflammatory cell type seen infiltrating tissues in the setting of obesity is the macrophage [14], a cell type often seen in a placental disc lesion called “chronic villitis” [13,15]. Chronic villitis (CV) is defined by the presence of a mixture of macrophages and lymphocytes—mostly T cells—infiltrating

* Corresponding author. Department of Reproductive Medicine, University of California, San Diego, 200 West Arbor Dr., #8433, San Diego, CA 92103, USA.
E-mail address: dlacoursiere@ucsd.edu (D.Y. LaCoursiere).

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chorionic villi [15]. While some are secondary to infection (i.e. with TORCH-related microorganisms such as CMV), the majority cannot be linked to any pathogen and are therefore thought to represent a transplantation rejection reaction, otherwise known as villitis of unknown etiology or VUE [13,15]. Where this lesion involves large areas of the placenta, it has been associated with intrauterine growth restriction and recurrent pregnancy loss [13,15]. In addition, and particularly when associated with obliterative fetal vascular lesions ("obliterative fetal vasculopathy"), CV is also known to be a risk factor for neonatal encephalopathy and cerebral palsy [15–17].

Evaluations of CV in the setting of maternal obesity have shown conflicting results; however, these studies have been relatively small in sample size (<50 per group): Challier et al. noted an increase in the number of resident macrophages in the placentas of obese women [18], while Roberts et al. were unable to see major differences in immune cell infiltration within the chorionic villi [19], instead, only noting increased expression of pro-inflammatory cytokines in such placentas. Larger studies have not addressed this question [11].

Pregnancy outcomes and placental pathology are also dependent on fetal sex [20]. Male neonates are often larger than females and have an increased risk of preterm birth and stillbirth, while pregnancies with female fetuses tend to be at a higher risk of preterm preeclampsia [21–23]. Relatively few studies have evaluated sex-related differences in placental pathology. Walker et al. reported placentas of male fetuses having significantly higher rates of velamentous insertion of umbilical cord and chronic deciduitis, and lower rates of villous infarction compared to those of female fetuses [24]. A relationship with fetal sex has not been described for either CV or fetal thrombosis.

This study aimed to evaluate placental pathology in the setting of pregravid obesity in patients delivering at or near term, with a focus on CV, as this is the main lesion involving infiltration of macrophages in the placental villi. Given the links between maternal obesity with diabetes and hypertensive diseases of pregnancy, as well as the association between fetal sex and pregnancy outcomes, this study explored the influence of these variables on placental pathology in the setting of maternal obesity. The hypothesis was that maternal obesity is linked to specific pathologic findings of the placenta, which differ based on fetal sex.

2. Materials and methods

The study, approved by the Human Research Protections Program Committee of the University of California San Diego (UCSD) Institutional Review Board, is part of a Perinatal Biospecimen Banking study, where both low- and high-risk pregnant patients are consented, and both clinical data as well as various biospecimens, including placental tissue, are collected. The subjects for this study were selected from amongst this study population based on the following criteria: delivery of a singleton, live-born infant at or after 35 weeks gestational age between January 1, 2010 to April 30, 2013; and documented maternal pregravid or early pregnancy weight (obtained prior to 14 weeks). Maternal demographic, anthropometric, and obstetric data, as well as neonatal outcomes data were abstracted from the electronic medical record. Placental examination, including gross and histologic examinations, were performed either through the hospital (for those with a clinical indication for placental exam) or through the research core (for those placentas without such indications).

2.1. Maternal data

Specific maternal factors included maternal age, ethnicity, pregravid BMI, BMI at delivery, gestational age, diabetes, hypertension and mode of delivery. The majority of Non-Hispanic women were White Non-Hispanic. Asian and Black participants comprised 4.4% and 2.4% of the study population, respectively. For calculation of all BMI measured weight and height were used. For pregravid BMI, measured weight under 14 weeks gestation was used. For BMI at delivery, measured weight at either the last prenatal visit or at admission for delivery was used. Maternal BMI was classified as normal weight (20–24.9 kg/m^2), class I obesity (30.0–34.9 kg/m^2), class II obesity (35.0–39.9 kg/m^2), or class III obesity (≥40.0 kg/m^2). For the majority of analyses, maternal obesity was used as a dichotomous variable. For dichotomous analyses, class 1 to 3 obesity were aggregated into one group. The diagnosis of diabetes included pre-gestational type 2 diabetes (T2DM) or gestational diabetes type 2 (GDMA2); patients with type 1 diabetes (T1DM) or gestational diabetes type 1 (GDMA1) were excluded. Patients with GDMA2 were identified by an abnormal 2-h or 3-h glucose tolerance test, and treated with oral medication or insulin therapy for adequate glycemic control. Hypertensive disorders were classified based on the following: Chronic Hypertension (CHTN), defined by high blood pressure persistently at or above 140/90 mmHg, diagnosed before 20 weeks gestation without proteinuria. Gestational hypertension (GHTN), defined by elevated blood pressure at or above 140/90 mmHg on at least two occasions at least 6 h apart after the 20th week of gestation in women known to be normotensive before pregnancy and before 20 weeks gestation without other signs or symptoms of preeclampsia based on the 2013 American Congress of Obstetricians and Gynecologists guidelines [25]. Preeclampsia or preeclampsia with severe features was defined based on ACOG criteria [25].

2.2. Neonatal data

Neonatal gender, birthweight (grams) and the APGAR scores at 1 and 5 min were recorded. Birthweight percentile (BW%) was adjusted for gender and gestational age based on the 1999–2000 US Natality Datasets [26,27]; category of growth was classified by the following defined as follows: small for gestational age (SGA) as birth weight of ≤10th percentile, normal for gestational age as birth weight between 11th and 89th percentile, and large for gestational age (LGA) as birth weight ≥ 90th percentile. Macrosomia was defined as birth weight greater than 4000 g [6,7,28,29].

2.3. Placental histopathology data

Placental examination was performed by a single pathologist (MMP) using standard protocols [13].

2.3.1. Gross examination

Size, weight, and lesions of the placental disc were recorded. Specifically, the weight of the unfixed disc was measured without attached cord and membranes. Placental weight percentile was adjusted for gestational age [30], and designated as "large" if it was ≥90th percentile for gestation. Placental efficiency was defined by the ratio of fetal to placental weight at delivery.

Fetal membrane (color and insertion) and umbilical cord (length, insertion site, and lesions) were also evaluated. "Umbilical cord abnormality" was defined based on factors associated with umbilical cord obstruction, and included abnormally long cord, hypertwisting (>3 twists per 10 cm), or the presence of true knot(s) [31].

For each placenta, the following sections were examined histologically: one section each of umbilical cord and membrane roll; any disc lesions; and two full-thickness sections of grossly-normal placental disc. All these sections were processed, embedded in paraffin, sectioned, and stained with hematoxylin and eosin (H&E)