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A systematic review of placental pathology in maternal diabetes mellitus

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ABSTRACT

Introduction: During a pregnancy complicated by diabetes, the human placenta undergoes a number of functional and structural pathologic changes, such as increased placental weight and increased incidence of placental lesions including villous maturational defects and fibrinoid necrosis. The pathologic findings reported have differed among studies, potentially reflecting differences in type of diabetes, study methodology, or glycemic control of study participants. Alternatively, these discrepancies may represent different biologic adaptations to distinct metabolic diseases.
Methods: We conducted a comprehensive review of English language citations in Pubmed and Embase using the keywords "diabetes", "placenta", AND "pathology". Abstracts were reviewed for relevance then full-text articles were reviewed in order to extract a comprehensive summary of current pathological findings associated with pregestational and gestational diabetes mellitus, as well as an understanding of the impact of glycemic control on placental pathology.
Results: Placental abnormalities most consistently associated with maternal diabetes are an increased incidence of villous immaturity, increased measures of angiogenesis, and increased placental weight.
Conclusions: The literature suggests that, despite similarities in placental abnormalities, differences in placental pathology may reflect differences in pathophysiology among different types of diabetes. Consequently, standardization of terminology used to define placental lesions is warranted. Moreover, further research is needed to investigate the impact of pathophysiology, glycemic control and clinical factors, such as infant sex, weight and race, on placental structure and function.

1. Introduction

The human placenta is the critical organ responsible for the facilitation of nutrient uptake, waste elimination, and gas exchange between mother and fetus [1]. The placenta is also a vital source of hormone production such as progesterone and human chorionic gonadotropin that maintain the pregnancy [1]. Consequently, placental dysfunction can lead to a number of adverse fetal outcomes [2,3]. Moreover, because the placenta reflects the metabolic milieu of both mother and fetus, it serves as a valuable tool for studying the metabolic perturbations that may take place during pregnancy, such as diabetes mellitus.

The extent to which maternal glycemic control contributes to placental abnormalities remains unclear. Literature demonstrates that, when maternal glucose levels are well-controlled, the placentas from women affected by diabetes are normal as evaluated by routine light microscopy [4,5]. However, several studies have identified histopathologic placental abnormalities among women even with well-controlled pregestational [6–8] and gestational diabetes [9,10]. Moreover, placental abnormalities associated with maternal diabetes have been inconsistently reported in the literature, perhaps reflecting population differences in sample size [6,11]; glycemic control [7,12]; study methodology [13,14]; prenatal care quality [15,16]; or diabetes types [6,17].

To our knowledge, there have been no systematic reviews evaluating the differences of placental histopathology between pregestational diabetes, defined as type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM); and gestational diabetes (GDM), defined as diabetes diagnosed during pregnancy that is not clearly overt diabetes [18]. Consequently, we have developed a

Abbreviations: GDM, gestational diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

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comprehensive systematic review of the current literature in order to critically examine the gross and histopathologic findings associated with dysglycemia in pregnancy. The literature will be discussed with respect to diabetes type, pregestational or GDM, as well as by the control groups under investigation and the placental derangements demonstrated.

2. Methods

2.1. Search strategy

Literature searches of MEDLINE (PubMed) and EMBASE databases were conducted through September 1, 2014 with the key terms “diabetes”, “placenta”, “pathology” and “histopathology”. Two investigators (JH and DD) independently reviewed titles, abstracts, and full-text articles. Additional articles were identified through searching the reference lists from included studies. Search results and included articles were verified by a third investigator (RB-L). Disagreements were resolved by consensus.

2.2. Eligibility criteria

Pre-specified inclusion criteria required that participants included pregnant women classified as having pregestational diabetes or GDM; the study compared findings in two or more comparison groups; and the outcome measure included gross or histopathologic placental abnormalities. Studies were excluded if they examined placental abnormalities in animals; were case-reports or review articles; were comprised of women with diabetes and other pregnancy complications such as preeclampsia or hypertension; did not have a valid comparison group; or did not specify diabetes type.

2.3. Data extraction and analysis

Data on population characteristics, diabetes class, and placental abnormalities were extracted. Two investigators performed the data extraction (JH and DD), which was then verified by a third investigator (RB-L). Because of the variability in GDM diagnostic criteria in use [18], data on the criteria used for defining GDM were also extracted. Because of the substantial heterogeneity in study methodology, placental abnormalities under investigation, and population characteristics, a quantitative meta-analysis of the data was not appropriate.

2.4. Exposure definitions

For the purposes of this systematic review, we categorized study findings by diabetes type as reported by the study authors. Pregestational diabetes is defined as either T1DM or T2DM before pregnancy. T1DM is characterized by a severe deficiency in insulin production due to the autoimmune destruction of islet cells in the pancreas [18]. Conversely, T2DM is a metabolic disorder characterized by insulin resistance and relative insulin deficiency [18]. Similar to T1DM, it is also characterized by hyperglycemia; persistent hyperglycemia from both T1DM and T2DM has been associated with a number of well-described adverse clinical sequelae, such as retinopathy, nephropathy, peripheral neuropathy, and diabetic encephalopathy [19–21]. These conditions reflect the damage hyperglycemia inflicts upon not only the nerves, but also the vasculature, which leads to impaired blood flow with subsequent end-organ damage. Consequently, the presence of maternal systemic vascular complications may also portend the impact to uterine vasculature affecting placental perfusion [22,23].

Table 1
White classification of diabetes in pregnancy.[a]

Class A	Abnormal glucose tolerance test at any age or of any duration treated only by diet therapy
A1	Gestational diabetes; controlled by diet and exercise
A2	Gestational diabetes; requires insulin
Class B	Onset at age 20 or older or with duration of less than 10 years
Class C	Onset at age 10–19 or duration of 10–19 years
Class D	Onset before age 10 or duration greater than 20 years
D1	Onset before age 10 years
D2	Duration over 20 years
D3	Calcification of vessels of the leg (macrovascular disease)
D4	Benign retinopathy (microvascular disease)
D5	Hypertension (not preeclampsia)
Class R	Proliferative retinopathy or vitreous hemorrhage
Class F	Renal nephropathy with over 500 mg/d proteinuria
Class RF	Criteria for both classes R and F
Class G	Many pregnancy failures
Class H	Evidence of arteriosclerotic heart disease
Class T	Prior renal transplant

[a] Data from Refs. [27,29].

GDM has been considered to be a transient insulin resistance potentially resulting from the influence of several pregnancy hormones, including progesterone, cortisol, placental lactogen, prolactin and growth hormone [24]. After delivery, the insulin resistance improves, although GDM has been associated with an increased risk of subsequent T2DM. Because the metabolic derangements in GDM are more pronounced in the latter stages of pregnancy [25], GDM is generally responsible for fewer birth defects than pregestational diabetes [26]. Nonetheless, GDM is associated with several fetal complications such as macrosomia and hypoglycemia; and maternal complications, including hypertension, preeclampsia, and an increased risk of Cesarean delivery [24].

Additionally, the White classification of diabetes in pregnancy, developed by Priscilla White in 1949 in order to predict perinatal outcomes [27], was used to aggregate populations in several studies included in this systematic review. These criteria, subdivided into different categories by the age of onset, duration of diabetes, and presence of vascular disease, are provided in Table 1. The original White classification did not include a category for GDM; however, Dr. White's 1965 and 1978 revisions expanded the definition to include GDM [28,29].

2.5. Outcome definitions

For the purpose of this systematic review, we categorized placental gross and histologic findings as reported by the study authors. Because placental gross and histologic findings varied among study papers, a true meta-analytical approach was not possible. However, we extracted data on whether or not definitions of placental variables were provided in the study and we listed these variables in the column, “Placental structure/abnormalities under investigation,” in Tables 2–4.

2.6. Methodological quality assessment

The study team assessed the methodological quality of the studies by comparing study design, inclusion criteria, and the blinding of investigators to pregnancy outcome or causation.

3. Results

3.1. Study characteristics

The selection algorithm for the 38 studies that met the inclusion and exclusion criteria for our systematic review is detailed in Fig. 1. Study characteristics, diabetes type, placental abnormalities examined, and population characteristics for studies in pregnancies affected by pregestational diabetes are summarized in Table 2. Nine of the 16 studies included in this systematic review examined women with T1DM compared to normoglycemic controls [7,12,17,30–35]. Two other studies identified women as having pregestational diabetes [8,36] while the remaining five studies defined the women by the White classification [6,11,27,37–39]. No studies were identified that specifically examined women with maternal T2DM compared to a normoglycemic population.

Study characteristics, diagnostic criteria, placental abnormalities examined, and population characteristics for studies of pregnancies complicated by GDM are summarized in Table 3. Seven studies examined placental gross or histomorphometric features in women with GDM compared to those with normoglycemia [9,10,14,40–43]. Diagnostic criteria for GDM were inconsistent across studies: two studies used Carpenter-Coustan criteria [10,14]; one study used the 1964 O'Sullivan and Mahan criteria [9]; one study used 2001 ADA criteria [43]; one study used the WHO criteria [40]; and two studies did not specify the diagnostic criteria used [41,42].

Study characteristics, diabetes type, placental abnormalities examined, and population characteristics for studies examining more than one type of diabetes are summarized in Table 4. Six studies compared findings across different White classifications with a normoglycemic control group [4,44–48]; five studies compared findings between pregestational and GDM with a normoglycemic control group [49–52]; one study compared findings between T1DM and GDM with a normoglycemic control group [53]; two studies examined differences between T1DM and T2DM [13,15]; and one study examined placental histomorphometry in women with GDM using race/ethnicity as the basis for comparison