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Placental Structural Abnormalities in Gestational Diabetes and When They Develop: A Scoping Review

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Abstract

Gestational diabetes mellitus (GDM) is defined as diabetes with onset or first recognition during gestation. It is a common complication of pregnancy that has become more prevalent over the past few decades. Abnormalities in fetal growth, including increased incidence of both large and small for gestational age babies, suggest placental dysfunction. The major goal of this scoping review is to determine what is known about abnormalities in placentas delivered from GDM pregnancies, and how early in gestation these abnormalities arise. A secondary goal is to review to what extent other selected factors, particular obesity, have been found to influence or modify the reported effects of GDM on placental development, and whether these are considered in the study of GDM placentas. PubMed and Scopus databases were searched using the key terms: "gestational diabetes AND (woman OR human) AND placenta AND (ultrasound OR ultrastructure OR imaging OR histology OR pathology). Studies of gross morphology and histoarchitecture in placentas delivered from GDM pregnancies consistently report increased placental size, villous immaturity and a range of vascular lesions when compared to uncomplicated pregnancies. In contrast, a small number of ultrasound studies have examined placental development in GDM pregnancies in the second, and especially, the first trimester. Relatively few studies have analyzed interactions with maternal BMI, but these do suggest that it may play a role in placental abnormalities. Further examination of placental development early in pregnancy is needed to understand when it becomes disrupted in GDM, as a first step to identifying the underlying causes.

Introduction

Gestational diabetes mellitus (GDM) is a common complication of pregnancy, and its prevalence is increasing worldwide [1]. GDM is defined as glucose intolerance with onset or first recognition in pregnancy, although as discussed below, the procedures and criteria for diagnosing GDM have changed over time and differ amongst institutions. Pregnancies complicated by GDM are more likely to result in adverse obstetric outcomes including preterm labor, caesarean-section, macrosomia and shoulder dystocia [2]. Even for infants born at normal weight, exposure to GDM has lifelong consequences for growth patterns,

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obesity risk and development of diabetes [3, 4]. Additionally, although fetal overgrowth is a widely recognized consequence of GDM, there are also more babies born small for gestational age (SGA) in GDM than in normoglycemic pregnancies, and pregnancies with SGA babies are at higher risk of poor fetal outcomes [5]. Collectively, these abnormalities in fetal growth point to placental dysfunction. As will be discussed, multiple histological abnormalities have been described in GDM placentas examined after delivery. However, it is not clear when in pregnancy these abnormalities arise, or even whether they precede or follow the onset of glucose intolerance. Improvements in imaging technologies have allowed visualization of placental features progressively earlier in gestation. The goal of this scoping review is to summarize what is known about placental abnormalities in delivered GDM placentas, and how early in gestation they arise. We also ask when in pregnancy placental development has been assessed in GDM, and whether findings from pre-term imaging studies can be connected to the structural differences observed in delivered GDM placentas histologically.

A secondary goal is to review other relevant factors that influence or modify the reported effects of GDM on placental development. Do studies consider or control for maternal obesity, a risk factor for GDM that can also independently affect placental development [6–8]? Are there meaningful distinctions between GDM and pre-gestational diabetes, or amongst GDM subtypes? Was mode of delivery considered? One potentially relevant factor to consider is variable definitions of GDM. Beginning in 1964, a 100g, 3h oral glucose tolerance test, with two or more abnormal values, based on maternal risk of developing diabetes postpartum was established for diagnosing GDM[9]. These threshold values were subsequently revised downward based on work from Carpenter and Coustan in 1982[10]. In 2010, the International Association of Diabetes in Pregnancy Study Group (IADPSG) recommended that a 75g oral glucose tolerance test (OGTT) be given, with just one value greater than 92, 180 and 153 mg/dL for fasting, 1, 2 and 3 h, respectively, considered diagnostic of GDM, based on the risk of perinatal complications [11]. The IADPSG guidelines have been adopted by the WHO and the American Diabetes Association and are used in much of the world[12]. However, the screening procedure recommended by the American College of Obstetricians and Gynecologists (ACOG) and followed widely in the United States and Canada is a 50g oral glucose challenge test, which, if glucose exceeds 140 mg/dL at 1h, is followed by a 100g OGTT in which two values greater than 95, 180, 155 and 140 mg/dL for fasting, 1, 2 and 3 h, respectively, are diagnostic of GDM. Additionally, GDM may be divided into type A1, controlled by diet and exercise, and type A2, dependent on insulin, based on the White classification system[13]. Where possible, the diagnostic criteria utilized each of the reviewed studies are noted in Table 1.

Methodology

A systematic search strategy was utilized, supplemented by additional references and keywords suggested by the initial search results. The PubMed and Scopus databases were each searched using the key terms: “gestational diabetes AND (woman OR human) AND placenta AND (ultrasound OR ultrastructure OR imaging OR histology OR pathology).” The search was conducted for articles published through July 13th, 2020 and 956 unique publications were returned. Publications that involve pregestational diabetes but exclude

GDM, that only feature GDM superimposed on other complications of pregnancy, animal studies, and studies that do not distinguish between overt, pre-gestational diabetes and gestational diabetes were excluded. Additionally, references were excluded if the full text was not available to the authors or was not available in English. Primary research articles were included if they describe placental morphology, histology or structure at the cell, tissue or organ level. An initial screen was conducted by one of two reviewers (EE or OT) to narrow the list to 196 potentially relevant results. Then, two independent reviewers (EE, OOT, LCS) conducted a detailed review of each of these papers, which identified 117 relevant, full-text publications for synthesis (Figure 1). Disagreements were resolved by a third, tie-breaking reviewer. For each publication identified, trimester of pregnancy assessed, whether maternal BMI was considered, GDM diagnostic criteria, mode of delivery, White classification and a description of the placental outcomes was recorded. Publications were then organized into categories. Some studies fit into multiple categories and were cross reviewed (Table 1).

Placental Size

GDM placentas are most consistently found to be larger than controls at term, in weight [17, 25, 31, 39, 47, 54, 64, 66, 78, 81, 89], volume [39, 64, 90], thickness, and diameter [17, 55, 64], although there are some exceptions [50, 53] placental weights below the 10th percentile are also more common in GDM [91]. The increase in volume is a result of increased parenchymal villous tissue and intervillous spaces, as well as extravillous trophoblasts, but not placental membranes or maternal decidual tissue, suggesting an increase in the functional trophoblast exchange area [39, 90, 92]. However, as discussed below, this is accompanied by changes in villous architecture that would likely reduce maternal-fetal exchange efficiency. Larger placental weight in GDM is a predictor of larger infant birth weight [35], which may reflect increased placental delivery of nutrients or may simply result from GDM independently increasing both fetal and placental growth. Results from 2D and 3D ultrasonography suggest that placental overgrowth generally arises in the second trimester in GDM, and worsens or becomes more prevalent as gestation progresses [20, 31, 57, 61, 76, 84]. No differences in placental volume have been detected in GDM pregnancies at 11–14 weeks, but they are significantly larger by 21–24 weeks [84]. Elevated placental thickness is likewise apparent by 24–28 weeks via ultrasound assessment, and continues to increase through term [20]. Abnormal placental thickness was more prevalent in GDM than in type I diabetic pregnancies [20].

These data suggest that placental size increases in tandem with increasing glycemia, as the majority of women diagnosed with GDM don’t meet the WHO definition of glucose intolerance before 24 weeks, although many have evidence of some level of hyperglycemia as early as the first trimester detected by OGTT, fasting glucose or HbA1C [93, 94]. At delivery, placental weights have been found to be directly proportional to the degree of glucose intolerance [46]; placental weights in women with GDM or pre-gestational diabetes are closer to those of uncomplicated pregnancies with good glycemic control [79, 95]. Placental weight also is inversely correlated with total caloric intake from protein, as estimated from food diaries over five days at 28–30 weeks in pregnancies diagnosed with GDM [24]. Maternal body mass index appears to contribute to placental overgrowth in

GDM, but does not fully explain it. While placental weight increases with BMI amongst women with GDM [36, 62, 75], and one study found elevated placental weights in GDM only in women with pre-gestational BMI > 30 and or gestational weight gain > 20 kg [36], others have shown that GDM results in greater placental weights even when comparing to BMI-matched controls [25].

At the cellular level, increased placental size is associated with changes in both trophoblast cell death and proliferation rates in delivered placentas, but there is essentially no information on these processes in GDM prior to delivery, while the placenta is still growing. Immunohistochemistry of term GDM placentas reveal elevated protein expression of markers of cytotrophoblast cell proliferation KI-67 and PCNA [82, 96], consistent with greater placental volumes. However, increased TUNEL staining, a more apoptotic gene profile, and greater caspase activity and expression have all been detected in GDM placentas at term [15, 49, 82, 97], although at least one study has reported a more anti-apoptotic protein profile in GDM pregnancies carrying large for gestational age (LGA) fetuses [96]. Placental autophagy, the process by which cell components are recycled for energy or growth, also has a controversial relationship to GDM. While autophagic vacuoles and autophagolysomes have been observed in GDM placentas by electron microscopy, increased placental expression of autophagic markers is reported in some studies but no difference or lower expression is reported in others [41, 96, 98].

Villous Structure

Placental villi first form at approximately four weeks of gestation (2 weeks post-conception), as columns of cytotrophoblast grow towards the outward edge of the primitive syncytial mass [99]. These columns fill with a mesenchymal core, and within a week, hemangioblastic cells, vascular precursors, begin to form cords within the villous cores [100]. Cords are transformed into blood-filled capillaries by the sixth week of gestation, with vasculogenesis continuing throughout the first trimester [101]. By the second trimester, stem villi, attached to the chorionic plate, branch into mostly intermediate villi, which are characterized by a nearly continuous cytotrophoblast layer, a relatively thick syncytiotrophoblast, and somewhat central capillaries. As the placenta matures well into the third trimester, these villi further branch to form the smaller terminal villi, characterized by a discontinuous cytotrophoblast layer, thinned syncytiotrophoblast, more peripheral capillaries, existing capillaries that continue to elongate and branch and a greater surface area-to-volume ratio [102] (Figure 2).

Villous immaturity is a common histopathological finding in GDM, with decreased number and total surface area of terminal villi, thickened basement membranes, and more centrally-located capillaries in term placentas [20, 21, 23, 30, 31, 40, 74, 86, 89, 91, 92]. These immature villi in GDM are also associated with abnormally formed and less numerous microvilli on the syncytiotrophoblast surface [15, 38, 56]. All of these changes increase the barrier to maternal-fetal exchange of oxygen and nutrients. The timeline of villous maturation in GDM vs. non-GDM placentas is not clear. Placental maturity in the second and third trimesters may be judged by ultrasound using the Grannum scale, which is based largely on the degree of folding of the chorionic plate, and the frequency of calcifications

and hyperechoic areas, particularly in the basal plate [103]. While ultrasound maturity has been found to relate to oxygen exchange efficiency in normal term placentas [104], detailed comparison found essentially no relationship between the classic histological features of placental maturation assessed after delivery and the ultrasound definition of maturity [105]. Nonetheless, GDM placentas appear immature by ultrasound criteria in the second and third trimesters [20]and ultrasound findings of placental immaturity after 26 weeks have a sensitivity of 84.8–88.6% and specificity of 87.5–88.3% for detection of GDM [59, 61]. When immaturity is assessed in combination with placental thickness and fetal characteristics, GDM prediction on the basis of ultrasound screening is both sensitive (90.9 – 93.2%) and specific (89.6–92%) [20, 59, 61].

Another villous structural abnormality observed in GDM is villous edema, which has been correlated with reduced placental function [31, 56, 64]. While the cause is unknown, increased expression of water channel aquaporin 9 has also been observed, suggesting a mechanism for the accumulation of fluid, though vascular abnormalities, or inflammation could also be responsible [81]. The degree of placental histological change is not directly correlated to the degree of hyperglycemia, suggesting there are other factors contributing to edema [31].

Alterations in villous structure are also observed in pre-gestational diabetes, although there is no consensus on whether it is worse [30], similar [65], or less severe [15, 86] than in GDM, with at least one study reporting accelerated villous maturation in pre-gestational diabetes [106]. These findings, along with the relatively early age at which villous maturation defects are detected in GDM, suggest that hyperglycemia may not be the major cause of delayed maturation, and many of the defects persist even when there is good glycemic control [42]. There are almost no data with which to assess the contribution of obesity to villous maturation defects in GDM, although placental microvillous abnormalities are less frequent following a management program that decreases gestational weight gain in non-obese women with GDM [38].

Vascular function and vascular lesions

GDM pregnancies exhibit increased incidence of placental vascular lesions (histological changes related to blood flow) in the third trimester [69, 89, 91]. Evidence includes fetal thrombotic vasculopathy (obstruction of arteries and veins in the fetal-side placental vasculature) [107], elevated fibrinoid deposition in intervillous spaces [21, 86, 108], and fibrinoid necrosis [14, 31, 55, 61, 109]. It has been proposed that higher incidence of intervillous thrombi is associated with localized hemorrhage, due to the presence of fetal hemoglobin within these blood collections, but the causes are unknown [18]. Some of the pathological findings in GDM placental villous vasculature, including pericyte detachment and pericyte ghost cells, are also observed in the retinal vasculature in patients with type I or type II diabetes [27, 67]. In a prospective study of over a thousand patients, GDM placentas had significantly higher rates of chorangiosis (elevated capillary density in terminal villi), and fetal thrombotic vasculopathy than uncomplicated pregnancies, but it should be noted that 80% of GDM placentas had normal histologic findings (absence of *any* type of pathological lesions) compared to just 72% of placentas from uncomplicated pregnancies

at or near term [108]. Thus, the vast majority of GDM term placentas lack such lesions, and placentas with pathologic findings do not always result in abnormal outcomes.

Although abnormalities in villous architecture are detectable in GDM only from the second trimester onward, and the precise branching of villous capillaries can only be assessed after delivery, 3D Power Doppler ultrasound has been used to detect reduced vascular indices and vascular flow indices in GDM placentas as early as 12 weeks gestation, suggesting that villous vascular abnormalities begin even prior to hyperglycemia [84]. In contrast, umbilical, pulsatility is not significantly different in GDM pregnancies and nitric oxide (NO) synthase activity is normal in cord artery and vein and chorionic plate artery and vein in delivered GDM placentas [22, 29].

Alterations in placental vascular function are also apparent at the cellular and molecular level. Loss of adherens junctions and reduced vascular-endothelial cadherin expression are consistent with reduced barrier function [19, 110]. *Ex vivo* contractility of chorionic vessels in response to adenosine is impaired, even in women with well controlled GDM, and expression of endothelin1 and endothelin-A, potent vasoconstrictors, is significantly decreased in whole term GDM placental lysates [28, 63, 111]. In contrast, *in vitro* smooth muscle relaxation and contractions in response to hypoxia-reoxygenation were exaggerated in arteries and veins isolated from GDM placentas after delivery [35]. Vasodilatory endothelial nitric oxide synthase (eNOS) activity is reduced in stem villous vessels from GDM placentas [29], while iNOS, which is not normally expressed in the placenta, is present in both endothelial cells and trophoblasts in GDM [68]. In culture, the migratory capacity and proliferative responses of vascular endothelial cells from GDM pregnancies are also impaired [83, 88]. Both arterial and venous villous endothelium exhibit global alterations in DNA methylation and gene expression, particularly in actin organization and pathways regulating cell morphology and barrier function [26] in the GDM placenta.

Other Pathologic Features

Other pathologic features have been observed in GDM placentas in one or more studies. GDM placentas exhibit higher central and peripheral elasticity by shear wave elastography, a measure of placental stiffness that correlates with histopathological changes like fibrosis [87, 112]. GDM placentas have more syncytial knots than controls [14, 56, 64, 85]. Although syncytial knots occur with increasing frequency as normal placentas mature, excessive numbers are associated with placental malperfusion [113]. Abnormalities are also observed at the ultrastructural level in term placentas from GDM pregnancies, particularly in mitochondria, although altered endoplasmic reticulum has also been reported [38, 42, 56, 65]. Mitochondrial abnormalities include swelling or dilation, fracturing, reduced matrix density and disrupted cristae [38, 51, 56, 65] (Figure 2). In cytotrophoblast cells, significantly reduced mitochondria numbers and size, as well as mitochondrial elongation were measured in placentas from both diet-controlled and insulin-controlled GDM pregnancies relative to controls, whereas mitochondrial density was reduced in both syncytiotrophoblast and fetal endothelium [114]. These structural abnormalities are consistent with the 50% reduction in mitochondrial respiration measured in A2 GDM

placentas compared to BMI -matched controls, and accompanying decreases in protein levels of mitochondrial electron transport chain complexes I,II,III and IV [115].

Studies of mitochondrial structure and function in GDM often do not account for BMI. However, mitochondrial abnormalities have been observed in fetal endothelial cells in GDM placentas even compared to placentas from obese controls [67]. In contrast, mitochondrial DNA copy numbers in maternal plasma, which provide at least an indirect indication of placental mitochondrial number and health, are significantly higher at term in GDM pregnancies when compared to normal weight controls, but not when compared to obese controls [116]. While there are understandably no studies of placental mitochondria in GDM pregnancies prior to term, mtDNA in maternal plasma can be measured at any gestational age. At 20 weeks, just as at term, there are higher circulating mtDNA levels in women with GDM compared to lean (BMI = 24.64 +/− 3.94) but not BMI-matched (BMI = 28.07 +/− 5.32) controls [117]. Thus, the increase in mtDNA probably reflects BMI more closely than GDM. Further, because mitochondrial numbers and function are reduced in GDM placentas at term, it is likely that these higher circulating mtDNA levels reflect cell death or loss of mitochondria in the second and third trimesters. Although placental mtDNA can be detected in maternal plasma in the first trimester [118], it has not yet been measured in pregnancies that go on to develop GDM. Thus, it is not known when in pregnancy mitochondrial abnormalities begin. However, strict management of GDM and improved glycemic control after diagnosis at 24–28 weeks reduced ultrastructural abnormalities by half [38], suggesting that some of the mitochondrial damage arises after the onset of hyperglycemia.

Discussion

Altogether, it is clear that GDM disrupts placental development, likely through hyperglycemia, and other, as yet unknown metabolic or endocrine mechanisms, such as insulin resistance. While placental overgrowth is common, so are structural abnormalities like villous immaturity and vascular dysfunction that are likely to offset the fetal growth-promoting effects of a larger placenta. The major goal of this review was to summarize the structural placental abnormalities that have been reported in GDM, and determine what is known about when in pregnancy these placental pathologies develop. The most consistently reported pathologies are summarized in Figure 2. We found that placental overgrowth is both the most frequently reported abnormality, and the one that could most convincingly be linked to hyperglycemia, through timing, occurrence in pre-gestational diabetes, and responsiveness to glycemic control. While placental overgrowth has been observed in GDM as early as the second trimester, there is as yet no evidence for this earlier in gestation.

In contrast, a variety of vascular abnormalities, including chorangiosis, fetal thrombotic vasculopathy, and intervillous fibrin deposition, and even altered contractile and vasodilatory responses have been reported in GDM placentas, but with more variation amongst studies. Relatively few studies in this area examine common endpoints, or utilize with common approaches. Limited evidence from imaging studies of pre-term placental morphology suggests that vascular abnormalities and maturation defects in the GDM placentamay begin even before 24–28 weeks, raising the possibility that sensitive measures of placental function may in the future be used to predict the disease. However, we were able to find

only one, relatively small (n<50) study examining GDM placentas by ultrasound in the first trimester[84]. Thus, there is a clear need for additional study of the placenta early in GDM pregnancies, to better understand when placental development is altered.

The secondary goal of this review was to discover to what extent other relevant factors that may modify the influence of GDM on placental development have been considered. While a number of studies did consider maternal BMI in their analyses, this remained the exception rather than the rule (Table 1). Results from studies that did consider BMI, however, suggest that it is a relevant factor that ought to be considered in future. Almost none of the studies in our search compared diet-controlled and insulin-treated diabetics when reporting placental outcomes (Table 1). While no meta-analysis or truly systematic comparison was made here, broadly similar placental findings were reported across studies regardless of which GDM diagnostic criteria were used. In conclusion, there is a consistent, broad evidence base supporting the idea that placental structure is disrupted in GDM, but there is still a need for studies that address when in development these disruptions occur and what additional factors influence them.

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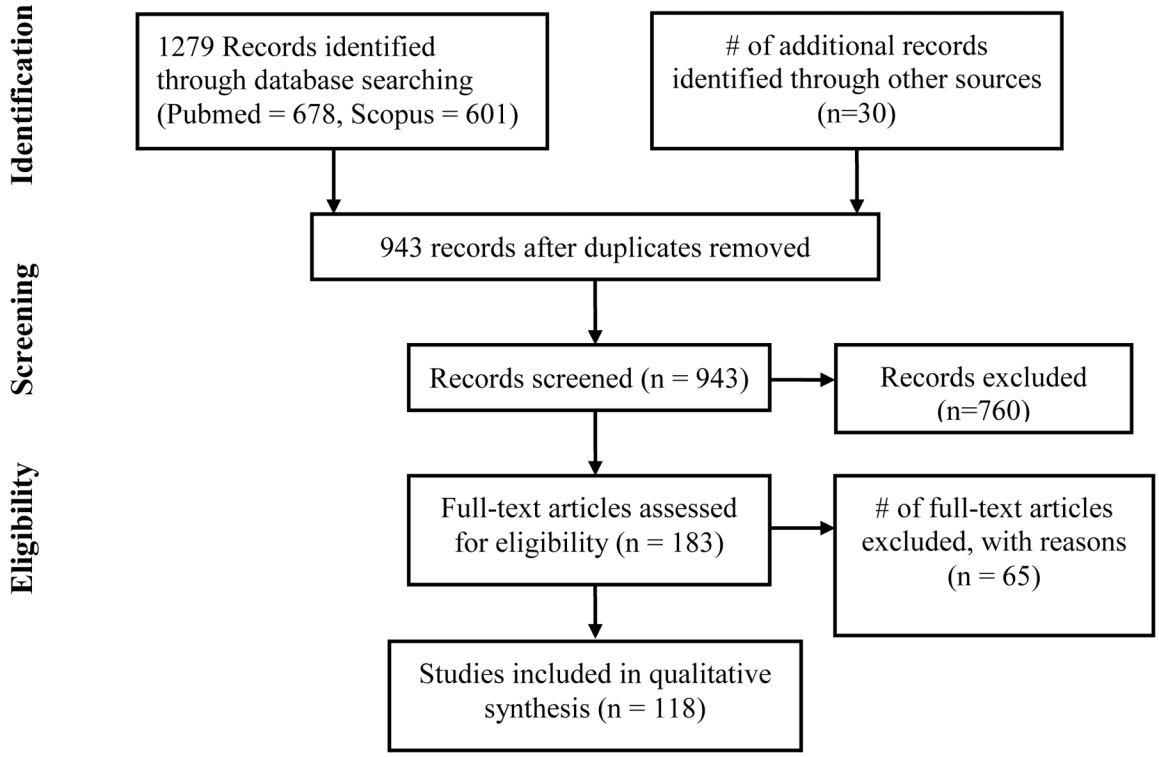

Figure 1:
Scoping review strategy

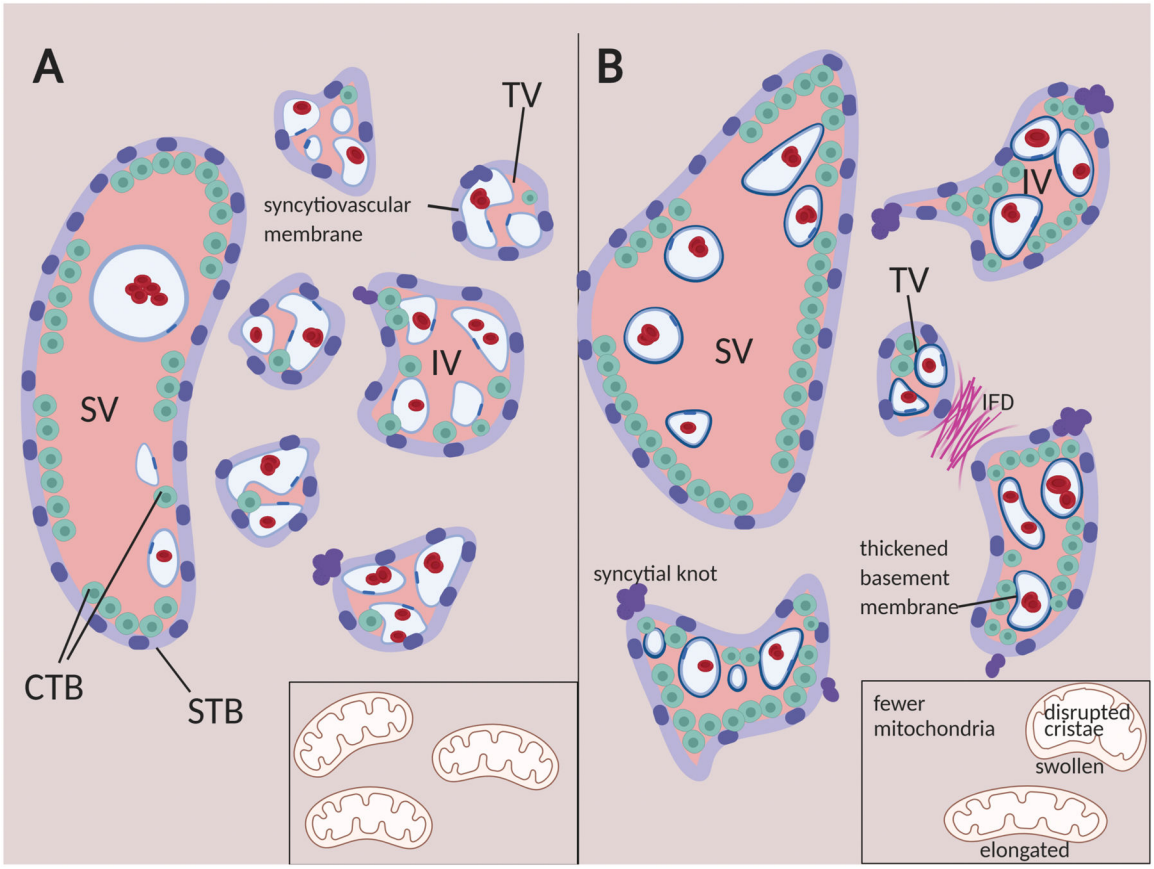

Figure 2:

Summary of histopathological anomolies in GDM placentas (A) Illustrated cross-section of placental villous tissue at term. (B) Abnormalities frequently observed in GDM placentas include villous immaturity (reduced terminal villous surface area, reduced syctyiovascular membranes, increased cytotrophoblast), vascular lesions like intervillous fibrin deposition (IFD), and excess syncytial knots. SV = stem villus, IV= intermediate villus, TV=terminal villus, CTB=cytotrophoblast, STB=syncytiotrophoblast. Inset: mitochondrial damage is also a feature of GDM placental trophoblast cells. Illustration created with BioRender.

Table 1:

Data Extraction table

Author Date	Gestational age range	Maternal BMI accounted for?	Stated GDM diagnostic criteria	Delivery mode accounted for?	GDMA1 vs A2 accounted for?	Subcategory (a-f)
Abou-Elghait et al. 2012 [14]	3rd, >37 weeks	no	WHO	no	no	histoarchitecture villous maturation fibrin deposition
Akarsu et al. 2017 [15]	3rd, at delivery	no	50g OGTT screen, 100g OGTT diagnostic	operative	A1 only	villous maturation
Arshad et al. 2015 [16]	at delivery	no	WHO	no	yes	Histoarchitecture, villous maturation, fibrin deposition
Ashfaq et al. 2005 [17]	3rd, “term”	no	not specified	no	no	placental size
Basnet et al. 2016 [18]	3rd	no	not specified	no	no	vascular function
Baumüller et al. 2015 [19]	3rd, at delivery	yes	not specified	no	yes	vascular function
Berceanu et al. 2018 [20]	2nd, 3rd, at delivery	no	not specified	no	no	placental size, histoarchitecture
Bhattacharjee et al. 2017 [21]	3rd, >37 weeks	no	Carpenter and Coustan	no	no	villous maturation, villous edema, fibrin deposition
Brown et al. 1990 [22]	3rd, 26–40 weeks	no	not specified	no	no	vascular function
Calderon et al. 2007 [23]	3rd, >34 weeks	no	ADA	no	no	villous maturation, vascular function
Chan et al. 2003 [24]	3rd, delivery	yes	WHO	no	no	placental size
Cosson et al. 2016 [25]	at delivery	yes	75-g OGTT with fasting plasma glucose ≥ 5.3 mmol/L and/or a 2-h ≥ 7.8 mmol/L	no	no	placental size
Cvitic et al. 2018 [26]	3rd, at delivery	no	WHO	no	no	vascular function
Deveci et al. 2013 [27]	3rd, 28–35 weeks	no	not specified	no	no	cellular/subcellular
Dieber-Rotheneder et al. 2012 [28]	3rd, 28–41wks	yes	75 g OGTT: > 95 1h, > 180 1h, >155 mg/dl 2h	no	no	vascular function
Dollberg et al. 1997 [29]	3rd, “term”	no	Carpenter and Coustan	no	no	vascular function
Dubova et al. 2011 [30]	3rd, >37 weeks	no	not specified	no	A1 only	villous maturation
Edu et al. 2016 [31]	2nd, 3rd	no	IADPSG	no	no	placental size, villous maturation, villous edema, fibrin deposition
Erkamp et al. 2020 [32]	1st, 2nd, 3rd	yes (lean)	Dutch guidelines: random glucose >11.0 mmol/l, fasting ≥7.0 mmol/l, or fasting 6.1–6.9 mmol/l with abnormal GTT	no	no	vascular function

Author Date	Gestational age range	Maternal BMI accounted for?	Stated GDM diagnostic criteria	Delivery mode accounted for?	GDMA1 vs A2 accounted for?	Subcategory (a-f)
Fadda et al. 2001 [33]	2nd, 3rd	no	National Diabetes Data Group (1979)	yes	yes	vascular function
Feng et al. 2016 [34]	3rd, “term”	no	75 g OGTT	no	no	cellular/subcellular
Figueroa et al. 1993 [35]	3rd, “term”	no	Carpenter and Coustan	no	no	vascular function
Ganer Herman et al. 2018 [36]	3rd, at delivery	yes	ACOG	yes	no	placental size
Georgiadis et al. 2014 [37]	2nd, 3rd, at delivery	yes	75g OGTT (fasting ≥ 4.8 mmol/l (until 2008) or ≥ 5.3 mmol/l (since 2009), ≥ 10.0 mmol/l 1h, and ≥ 8.6 mmol/l at 2h	no	no	vascular function
Han et al. 2016 [38]	3rd, at delivery	yes	75g OGTT -fasting glucose >92 mg/dL (5.1 mmol/L); 1h> 180 mg/dL (10.0 mmol/L); 2-h > 153 mg/dL (8.5 mmol/L)	no	no	villous maturation
Heidari et al. 2019 [39]	3rd, >37 weeks	no (not different between groups)	ACOG/ Carpenter and Coustan	matched	no	placental size
Huynh et al. 2015 [40]	3rd	yes	Carpenter and Coustan	no	no	histoarchitecture, villous maturation
Ji et al. 2017 [41]	3rd, at delivery	no	fasting glucose >5.1 mM or 1h OGTT >10.0 mM, or 2h OGTT >8.5 mM.	no	no	cellular/subcellular
Jones et al. 1976 [42]	3rd, >37 weeks	no	not specified	no	no	histoarchitecture
Jones et al. 1993 [43]	3rd, >37 weeks	no	not specified	no	no	vascular function
Kleiner et al. 2020 [44]	3rd, at delivery	no	ACOG	no	no	histoarchitecture
Kovo et al. 2016 [45]	3rd, “term”	no	ADA	matched	yes	placental size, histoarchitecture, villous maturation
Kozłowska-Rup et al. 2014	not specified	no	WHO	operative	A1 only	cellular/subcellular
Lao et al. 1997 [46]	3rd, at delivery	no	WHO (1980)	no	no	placental size
Lao et al. 2001 [47]	3rd, at delivery	no (groups not different)	WHO	no	no	placental size
Loegl et al. 2017 [48]	3rd, at delivery	yes	75 g OGTT, two or more >92 g/l fasting, >180 g/l 1 h, >153 g/l 2 h	no	no	vascular function
Magee et al. 2014 [49]	at delivery	no	ADA	operative	no	cellular/subcellular
Makhseed et al. 2004 [50]	3rd, at delivery	no	75g OGTT fasting >5.3 mmol/L or 2h >8.5 mmol/L	no	no	placental size
Mando et al. 2018 [51]	3rd, “term”	yes	OGTT (not otherwise specified)	operative	no	cellular/subcellular

Author Date	Gestational age range	Maternal BMI accounted for?	Stated GDM diagnostic criteria	Delivery mode accounted for?	GDMA1 vs A2 accounted for?	Subcategory (a-f)
Mayhew 1998 [52]	1st, 2nd, 3rd	no	not specified	no	yes	villous maturation, vascular function
Mayhew and Sisley 1998 [53]	3rd, >37 weeks	controlled	not specified	no	yes	placental size, fibrin deposition
McNamara et al. 2014 [54]	3rd, >37 weeks	yes	not specified	yes	no	placental size
Memon et al. 2015 [55]	3rd, “term”	no	not specified	no	no	placental size, histoarchitecture, fibrin deposition
Meng et al. 2015 [56]	3rd, “term”	no	ADA	operative	no	histoarchitecture, villous maturation, villous edema, fibrin deposition
Pala et al. 2016 [57]	2nd, 3rd	no	WHO	no	no	placental size, histoarchitecture
Pathak et al. 2010 [58]	3rd, >37 weeks	no	WHOhis	no	no	placental size
Pathak et al. 2011	3rd, >34 weeks	no	WHO	no	no	histoarchitecture
Patil et al. 2019 [59]	2nd, 3rd	no	Diabetes in Pregnancy Study group India (DIPSI)	no	no	villous maturation
Pavlova et al. 2020 [60]	not specified	no	not specified	no	no	histoarchitecture
Perovic et al. 2012 [61]	2nd, 3rd > 24 wks	no	ADA	not applicable	no	placental size, vascular function
Ramos et al. 2016 [62]	at delivery, ≥23 weeks	yes	NDDG	no	yes	placental size
Razak et al. 2018 [63]	3rd, >37 weeks	no	fasting ⩾5.6mmol/L or a 2h ⩾7.8mmol/L	operative	no	vascular function
Saha et al. 2014 [64]	3rd, at delivery	No	fasting glucose >126 mg/dl, random >200 mg/dl, or 100g OGTT	no	no	placental size, villous edema, fibrin deposition, vascular function
Sak et al. 2013 [65]	3rd, >28 weeks	no	not specified	no	no	histoarchitecture, villous edema, fibrin deposition
Salafia et al. 1989 [66]	3rd, >37 weeks	no	not specified	no	no	placental size vascular function
Samuel et al. 2014 [67]	3rd, “term”	no	fasting glucose ⩾92mg/dL and 1 h ⩾ 180mg/dL and 2 h ⩾ 153mg/dL	vaginal	no	vascular function
Schönfelder et al. 1996 [68]	3rd, “term”	no	NDDG criteria	no	no	vascular function
Scifres et al. 2017 [69]	3rd, at delivery	yes	Carpenter-Coustan	no	no	vascular function
Sharma S.et al. 2014 [70]	3rd, >36 weeks	no	fasting >90mg/dL or random >105 on first visit plus screening at 12–13 wks and 24–28 weeks	no	no	fibrin deposition, villous immaturity
Soygur et al. 2016 [71]	1st (4–9w) and at delivery (not specified)	yes	fasting glucose >92 mg/dl, 75g OGTT 1 hour >180 mg/dl, and 2 hours >153 mg/dl	operative	A2 only	cellular/subcellular

Author Date	Gestational age range	Maternal BMI accounted for?	Stated GDM diagnostic criteria	Delivery mode accounted for?	GDMA1 vs A2 accounted for?	Subcategory (a-f)
Stanek et al. 2007 [72]	2nd,3rd	no	not specified	no	no	histoarchitecture
Stanek et al. 2014 [73]	2nd, 3rd	no	not specified	no	no	histoarchitecture
Stoz et al. 1988 [74]	3rd, >37 weeks	no	100g OGTT (J.B O'Sullivan criteria)	no	no	villous maturation, vascular function
Strøm-Roum et al. 2016 [75]	3rd, at delivery	yes	2-h 75-g OGTT with glucose ≥7.8 to <11.1 mmol/L	no	no	placental size
Surányi et al. 2016 [76]	2nd, 3rd, 15–28 weeks	no	WHO	not applicable	no	placental size
Taricco et al. 2009 [77]	3rd, at delivery	no	ACOG/ Carpenter and Coustan	operative only	no	placental size
Taricco et al. 2003 [78]	3rd, >36 weeks	no	ACOG/ Carpenter and Coustan	no	no	placental size
Thunbo et al. 2018 [79]	3rd, >35 weeks	yes	not specified	no	no	placental size
Tramontana et al. 2018 [80]	1st	yes	IADPSG	no	no	vascular function
Vilariño-García et al. 2016 [81]	3rd, "term"	no	ADA	operative only	no	placental size
Visiedo et al. 2017 [82]	3rd, "term"	no	NDDG (1979)	operative only	no	cellular/subcellular
Wang et al. 2019 [83]	3rd, "term"	no	fasting >92 mg/dl and 1h >180 mg/dl or 2h >153 mg/dl on OGTT	no	no	vascular function, cellular/ subcellular
Wong et al. 2019 [84]	1st, 2nd	no	National Diabetes Data Group Criteria	no	no	placental size, vascular function
Yavuz et al. 2015 [85]	3rd, "term"	no	OGTT ≥140 mg/dL	no	no	histoarchitecture
Younes et al. 1996 [86]	3rd, >37 weeks	no	not specified	no	no	villous maturation
Yuksel et al. 2016 [87]	3rd	yes	ACOG/Carpenter and Coustan	no	yes	Histoarchitecture, vascular function
Zhou et al. 2016 [88]	3rd, >37 weeks	no	WHO/IADPSG	operative only	no	vascular function