Placental abnormalities in type 1 and type 2 diabetes mellitus: a systematic review and metaanalysis of shear wave elastography

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OBJECTIVE: This study aimed to describe the placental changes occurring in women with preexisting diabetes mellitus and to determine if elastography can detect placental changes in vivo.

DATA SOURCES: PubMed, Embase, Medline, and Cochrane were searched to identify English language studies published until July 2020.

STUDY ELIGIBILITY CRITERIA: 1) For key question 1, studies that described histopathologic changes in placentas from women with known diabetes mellitus and 2) for key question 2, those that described structural—placental changes detectable by elastography in high-risk pregnancies (eg, those complicated by preeclampsia and/or fetal growth restriction), were included.

METHODS: For key question 1, we grouped placental pathologies using the Amsterdam International Consensus Group definitions. For key question 2, we conducted a metaanalysis including all data from studies reporting placental stiffness in meters per second (m/s) or kilopascals (kPa). The mean difference (95% confidence interval) was calculated using a random effects model.

RESULTS: Data were extracted from 14 studies of placental histopathology in women with known diabetes. In this group, a wide variety of placental histopathologic changes are described, though none are considered pathognomonic. The histopathologic changes including maternal vascular malperfusion, fetal vascular malperfusion, and/or infectious/inflammatory/other changes were divided into 3 broad categories on the basis of presumed etiology. A total of 15 studies reported the placental stiffness scores in women with a high-risk pregnancy vs those with a normal pregnancy. Only 1 reported stiffness scores for placentas in women with preexisting diabetes mellitus (N<10 women). Pooled analysis of 14 studies with available data included 478 "high-risk pregnancies" and 828 control or healthy pregnancies. Maternal-derived pathologies resulted in higher placental stiffness (mean difference 4.5 kPa [95% confidence interval, 3.16−5.87]) compared with control or healthy pregnancies. Fetal-derived pathologies also resulted in higher placental stiffness (mean difference of 6.5 kPa [95% confidence interval, 1.08−11.86]) compared with control or healthy pregnancies.

CONCLUSION: Shear wave elastography may provide an in vivo approximation of placental histopathology in women with certain kinds of high-risk pregnancies. A high-risk pregnancy may involve maternal- and fetal-derived pathologies. Further studies, particularly in women with preexisting diabetes, are needed to confirm this observation.

Keywords: fetal growth restriction, placenta, placental histopathology, preeclampsia, preexisting diabetes mellitus, stiffness

The prevalence of type 1 diabetes mellitus [DM] is slowly increasing worldwide,[1−3] although more concerning is the rising global prevalence of type 2 diabetes mellitus, particularly among children and adolescents. This trend continues for women of childbearing age, with the prevalence of type 2 DM in pregnancy more than doubling[4] in recent decades and leading to early pregnancy losses.[5,6] The largest studies of women with DM in pregnancy have been conducted in the United Kingdom.[7,8] The National Pregnancy in Diabetes (NPID) audit[7] included 17,375 pregnancy outcomes from 15,290 pregnant women with type 1 or type 2 DM. The NPID findings demonstrate higher rates of major congenital malformations, birthweight extremes, and perinatal mortality

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Ethics approval was not necessary to undertake our systematic review of the literature.

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AJOG MFM at a Glance

Why was this study conducted?

Diabetes mellitus before conception may contribute to pregnancy complications including preterm birth, preeclampsia, and birthweight extremes. However, any associated role of the placenta is not fully understood. We conducted a systematic review of placental histopathology (and stiffness) in pregnancies affected by preexisting maternal diabetes mellitus.

Key findings

In vivo shear wave elastography reveals that placental stiffness scores are higher in women with preeclampsia and fetal growth restriction. However, data from women with diabetes mellitus are limited.

What does this add to what is known?

Placental histopathology findings in women with preeclampsia and fetal growth restriction have been described well previously. This study shows that women with preexisting diabetes mellitus may have similar placental histopathology. A unifying placental origin for adverse pregnancy outcomes across these groups may exist. Further studies of placental stiffness and function are needed in women with preexisting diabetes mellitus.

(including stillbirth or neonatal death). Higher rates of perinatal mortality are reported in Australia,[9,10] France,[11] The Netherlands,[12] and Denmark.[13] Other studies show equally high rates of preeclampsia[14] and preterm delivery.[15–18]

In early pregnancy, the cytotrophoblast invades the endothelial surface of maternal spiral arteries to establish a complex maternal-fetal vascular network. This crucial step sets the stage for the remainder of the pregnancy and has been implicated as a key pathway leading to preeclampsia.[19] It is likely that preexisting type 1 or type 2 DM compromises these early crucial steps in placental development.[20,21] Essential placental functions include gas exchange, provision of macro- and micronutrients, acting as a reservoir for byproducts of fetal metabolism, provision of immune protection with maternal antibodies, and endocrine effects enabling maternal adaptation to pregnancy.[22] Disruption to any of these (owing to DM) can affect the mother or fetus and may be evident in placental histopathology.

There are numerous published studies of placental elastography examination in the second and third trimesters, but none of these recruited women with preexisting DM. The authors note that no adverse safety concerns have been observed in any of the published literature to date. Shear wave elastography (SWE) is a technique that uses an acoustic radiation force pulse sequence to generate shear waves in a region of interest. These shear waves propagate perpendicular to the ultrasound beam. Measuring the velocity of shear waves is an absolute measure of the tissue's elastic properties. Simply put, high velocity shear waves are seen in rigid tissues, whereas lower velocities are seen in softer tissues. The clinical application of SWE to enhance pregnancy care is currently limited to observational research, ie, there are no studies to date utilizing SWE of the placenta for clinical decision-making. The purpose of this review is to provide an overview of the possibilities of SWE for use in future pregnancies with known diabetes, including lessons learned from other studies using SWE.

Methods

To guide this review, we developed 2 key questions as follows: (1) what placental changes occur in women with diabetes? and (2) can elastography detect placental changes in vivo?

The full details of all search terms are provided in Appendix S1 Supplementary Material.

The 2 systematic searches were performed according to the Preferred Reporting Items for Systematic Reviews and Metaanalyses (PRISMA) guidelines.

Our review protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020188532).

Data sources, study selection, and risk of bias assessments

For each key question, we searched multiple information sources, including The Cochrane Library, MEDLINE, EMBASE, and PubMed. For both the key questions, we included English language reports of any study type, including randomized controlled trials, cohort studies, case–control studies, cross-sectional studies, case reports, and case series. For histopathology, we limited our search to DM diagnosed before conception. For placental stiffness, we included only those studies reporting values in meters per second (m/s) or kilopascals (kPa).

Two review authors (A.G. and J.I.) independently reviewed the abstract and title of every record retrieved to determine which studies should be assessed further. Both the authors then conducted full-text screening to identify the items for final inclusion and full-text review. Disputes about inclusion were resolved by discussion between the 2 authors (A.G. and J.I.). Disagreements were resolved with review from a third author (D.S.).

To assess risk of bias in key question 1, we have used a quality assessment tool previously published by Murad et al.[23] Some elements of the Murad tool are specifically related to intervention studies, so these were omitted for the purpose of our quality assessment.

To assess risk of bias in key question 2, we used a modified quality assessment tool taken from the United States National Institutes of Health and is available from <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>; it specifically relevant to case series.

Data extraction

For key question 1, we collected data on population characteristics, year of publication, total number of patients examined, diabetes type, and histopathology

description. Investigators attempted to separate these "diluted groups" insofar as possible where participants with preexisting DM were grouped together with other participants (such as those with gestational diabetes mellitus [GDM]).

We collected data on histopathologic findings under 37 different features[24] grouped where possible under (1) maternal vascular malperfusion, (2) fetal vascular malperfusion, and/or (3) infectious/inflammatory/other features. These umbrella categories have been broadly described by the Amsterdam International Consensus Group in their consensus statement.[25] The Amsterdam group developed their statement to encourage more uniform reporting of placental changes worldwide. We observed and corrected for common nomenclature, eg, there may be multiple descriptors for the same underlying pathologic appearance. Tenney-Parker changes are equivalent to increased syncytial knots. For key question 1, 2 investigators performed the data extraction (J.I. and A.G.).

For key question 2, we collected information regarding year of study, country of origin, diagnosis to qualify a high-risk pregnancy, gestational age at time of elastography, elastography technique, number of cases of high-risk pregnancies, number of cases used as controls, and stiffness scores (data were collected in m/s or kPa and converted to kPa for analysis). The qualifying diagnosis for a "high-risk" pregnancy was divided into maternal diseases: these included hyperglycemia (type 1 and type 2 DM, GDM, and other hyperglycemia not fulfilling those diagnoses), hypertension, fetal growth restriction, collagen diseases in the mother, or rhesus alloimmunization. Fetal diseases were grouped separately and included single umbilical artery, fetal structural anomalies, placenta accreta spectrum, and placenta previa. For key question 2, two investigators performed the data extraction (J.I. and A.G.).

Data synthesis and analysis

For key question 1, the findings are summarized narratively and in bar graph format. The bar graphs have been grouped according to the Amsterdam Consensus Group categories[25] in an attempt to align with future research reports.

For key question 2, a metaanalysis of placental stiffness scores for "high-risk" vs control pregnancy was performed, as this was the only homogenous and quantitative outcome available for collection. Stiffness scores collected as meters per second (m/s) were converted to kPa for the purposes of metaanalysis. We conducted 2 separate metaanalyses (maternal pathologies and fetal pathologies) consistent with umbrella categories defined by the Amsterdam International Consensus Group.

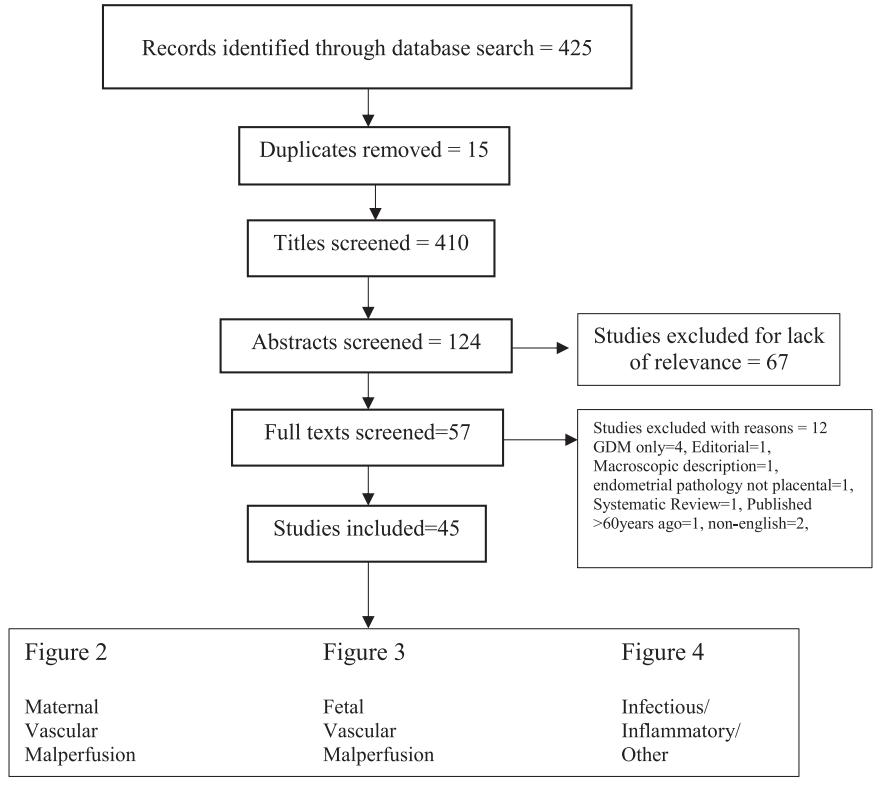
The results were pooled using Review Manager (RevMan) software, version 5.4 (The Cochrane Collaboration 2020). Where studies reported multiple groups with a shared control group, a single pairwise comparison was created using the RevMan calculator. The effect size was calculated using the mean and standard deviation of the stiffness values of placentas in high-risk and normal pregnancies. For studies that reported a median with interquartile range or a median with minimum and maximum, we estimated the mean and standard deviation using the method proposed by McGrath et al.[26] A random effects model was used to analyze the data. The mean difference and 95% confidence interval (CI) were used to report the overall effect size. Heterogeneity was assessed using the I^2 statistic, with values at 25%, 50%, and 75% considered as low, medium, and high heterogeneity, respectively.[27]

Results

Key question 1

Study selection. We have summarized our study selection process in Figure 1. In brief, for key question 1, our initial search strategy yielded 425 studies. After removal

FIGURE 1
PRISMA flow diagram for the review (key question 1)



PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis.

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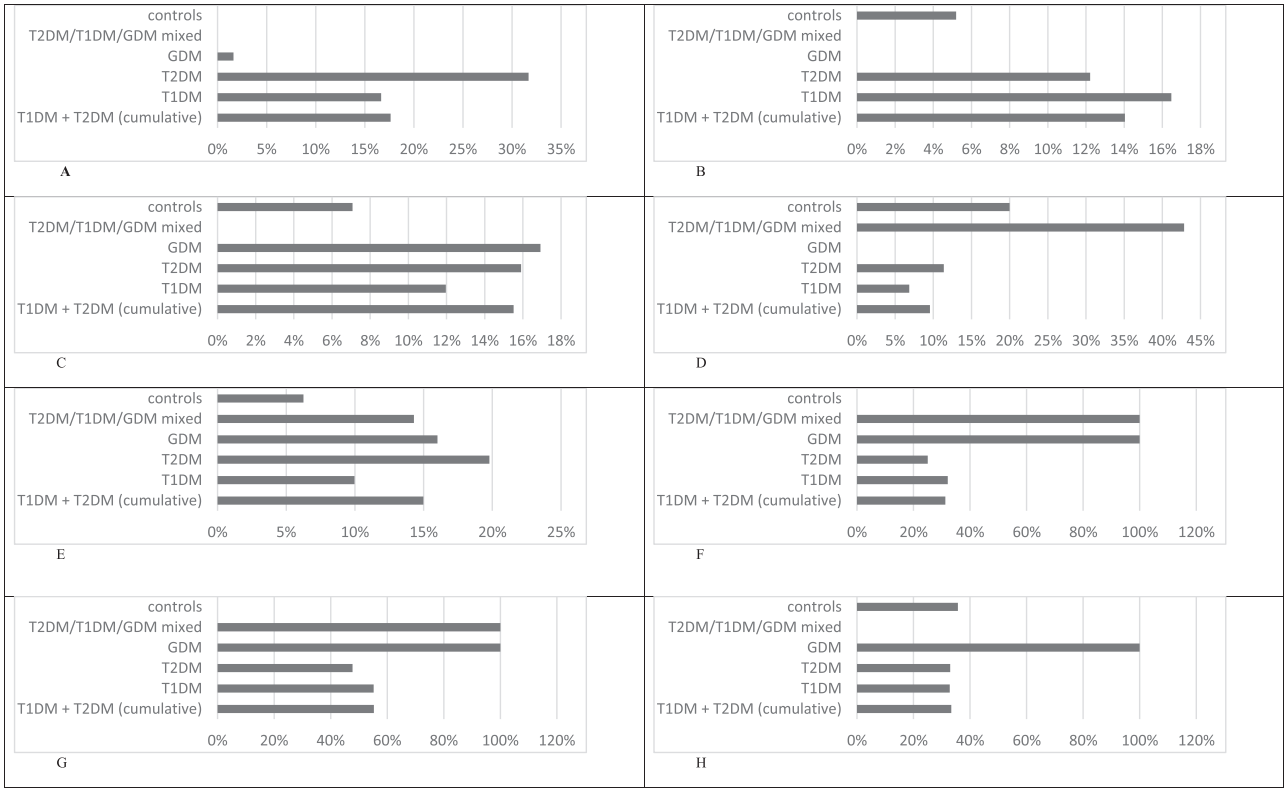
FIGURE 2
Histopathologic features related to maternal vascular malperfusion



A, Decidual vasculopathy in placenta from women with either T1DM or T2DM (n=720), GDM (n=248), T1DM (n=180), and T2DM (n=243). **B**, Accelerated villous maturity in placenta from women with either T1DM or T2DM (n=513), T1DM (n=170), T2DM (n=221), and controls (n=77). **C**, Intervillous thrombi in placenta from women with either T1DM or T2DM (n=464), GDM (n=130), T1DM (n=117), T2DM (n=176), and controls (n=99). **D**, Subchorionic hematoma or subchorionic fibrin deposition in placenta from women with either T1DM or T2DM (n=293), T1DM (n=117), T2DM (n=176), and mixed groups (n=21). **E**, Parenchymal infarct in placenta from women with either T1DM or T2DM (n=674), GDM (n=250), T1DM (n=291), T2DM (n=288), mixed groups (n=21), and controls (n=48). **F**, Perivillous fibrin in placenta from women with either T1DM or T2DM (n=390), GDM (n=2), T1DM (n=134), T2DM (n=176), and mixed groups (n=19). **G**, Prominent septa and/or basal plate in placenta from women with either T1DM or T2DM (n=340), GDM (n=2), T1DM (n=134), T2DM (n=176), and mixed groups (n=19). **H**, Tenney-Parker changes or syncytial knots in placenta from women with either T1DM or T2DM (n=456), GDM (n=2), T1DM (n=134), T2DM (n=176), and controls (n=14).

GDM, gestational diabetes mellitus; *TIDM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

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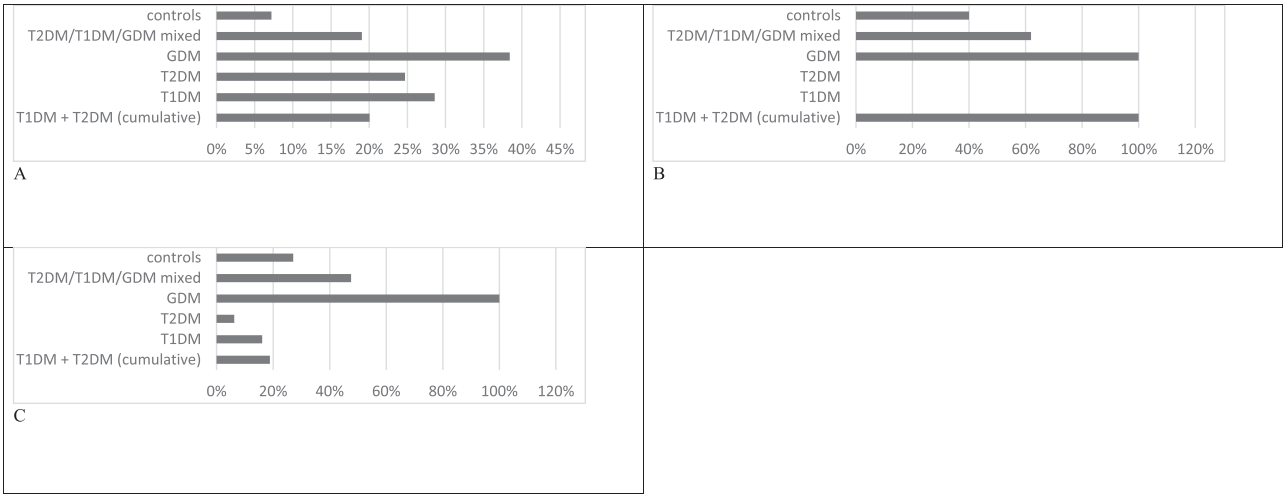
of duplicates and irrelevant studies, 45 studies were finally identified. Many of the studies identified for full-text analysis reported electron microscopy techniques or used special stains and immunohistochemistry; these are specialized (predominantly) research techniques and are not used in standard placental examination. These studies (n=31) were therefore excluded from bar graph analysis, but their major findings are summarized in Table S1 (Supplementary Material). Of 45 full-text reports identified, data from 14 are included in the bar graphs (Figures 2–4).

Study characteristics. Table 1 summarizes the characteristics for the 14 studies included in response to key question 1. Studies of placental histopathology in women with diabetes have been published over a long time period between 1969 and 2017. Many studies pooled participants into groups despite varying degrees of hyperglycemia. For example, some populations with preexisting diabetes before conception are "diluted" by including participants with "mild hyperglycemia," impaired glucose tolerance, GDM, or overt diabetes in pregnancy (ODIP).

Risk of bias of included studies. Two investigators (J.I. and A.G.) independently assessed each domain in the Murad tool to provide an overall rating of study quality. The complete quality assessment is shown in Tables S4 and S5 (Supplementary Material).

Synthesis of results. Total 16 bar graphs using cumulative data extracted from 14 studies have been shown (Figures 2–4). The characteristics of included studies have been summarized in Table 1. These 16 bar graphs (from a possible 37 placental pathologies

FIGURE 3
Histopathologic features related to fetal vascular malperfusion



A, Chorangiosis or chorangioma or increased villous capillaries or chorangiomatosis in placenta from women with either T1DM or T2DM (n=544), GDM (n=250), T1DM (n=238), T2DM (n=243), mixed groups (n=21), and controls (n=125). **B**, Villous congestion in placenta from women with either T1DM or T2DM (n=47), GDM (n=2), mixed groups (n=21), and controls (n=10). **C**, Avascular villi in placenta from women with either T1DM or T2DM (n=446), GDM (n=2), T1DM (n=192), T2DM (n=176), mixed groups (n=21), and controls (n=48).

GDM, gestational diabetes mellitus; *TIDM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

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outlined by Starikov et al)[24] were chosen as the most clinically relevant to a general surgical pathologist and most consistently reported placental findings across all study types. Data for control groups were not available for many of the studies. We focused on placental findings in women with preexisting DM. Thus, the data presented included only a limited number of women with GDM.

Maternal vascular malperfusion findings of decidual vasculopathy were more frequently seen in women with preexisting DM than in those with GDM (Figure 2, A). Accelerated villous maturation was frequently seen in women with type 1 and/or type 2 DM but was far less evident in healthy controls (Figure 2, B). The frequency of intervillous thrombi did not vary according to type of DM (type 1 vs type 2 vs GDM) but was seen less commonly in healthy controls (Figure 2, C). Placental infarcts were most common in women with type 2 DM (Figure 2, E), and this was similar to decidual vasculopathy (Figure 2, A). Perivillous fibrin and prominent septa and/or basal plate have been reported in women with type 1 or type 2 DM. However, control groups were not available for comparison. Tenney-Parker changes (also known as syncytial knots) were not more frequent in women with preexisting DM.

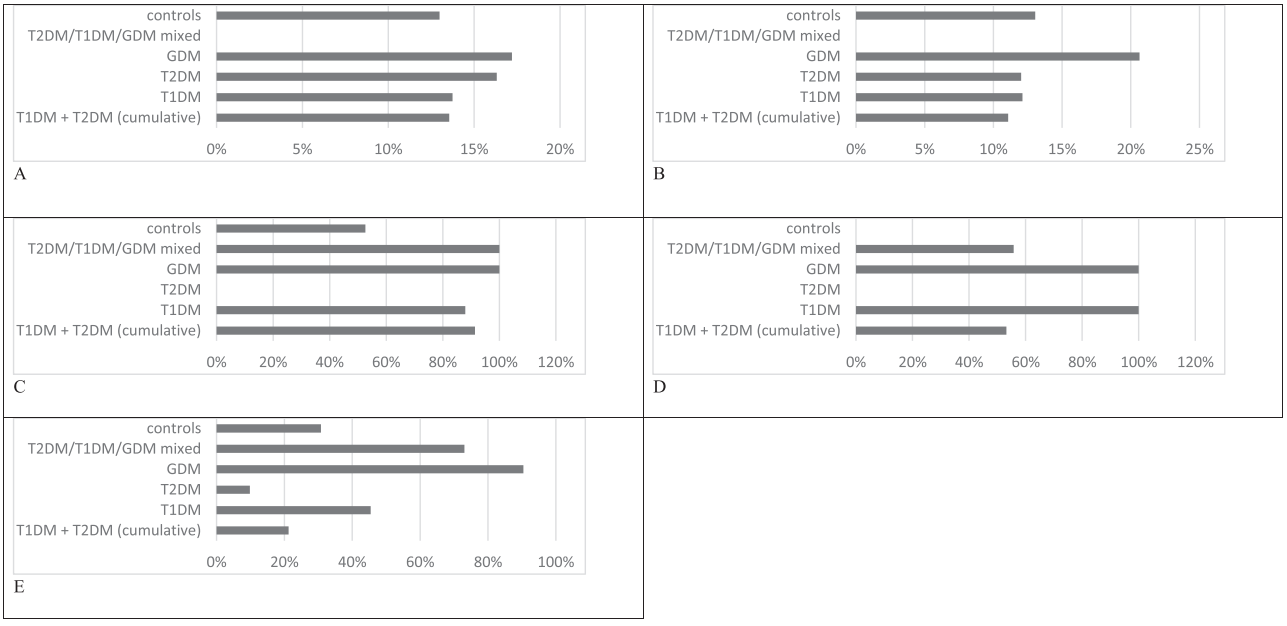
Changes within the fetal vascular compartment (possible fetal vascular malperfusion) were also seen for women with preexisting DM. There were increased villous capillaries and increased villous congestion than in healthy controls (Figures 3, A and B). Avascular villi in women with type 1 and/or type 2 DM were similar to healthy controls (Figure 3, C). Several other placental findings not grouped into either maternal or fetal vascular malperfusion were reported. Of these, fibrinoid necrosis stood out, as it was far more common in women with hyperglycemia than in healthy controls.

Key question 2

Study selection. Our initial search strategy yielded 456 studies. After removal of duplicates, 302 titles were screened for relevance, leaving 33 abstracts for review. After abstract review, 6 studies were excluded owing to lack of relevance. A further 12 were excluded after full-text review (details have been provided in Figure 5). A total of 15 studies were finally identified.

Study characteristics. We identified 15 studies across a variety of maternal and fetal pathologies (Table 2 and Figures 6 and 7), of which 14 were included in the metaanalysis (data were requested from the authors of the 15th study[28], but no reply was received). The types of "high-risk pregnancy" included hyperglycemia, intrauterine growth restriction (IUGR), gestational hypertension, preeclampsia, placenta previa, placenta accreta spectrum, collagen diseases (including autoimmune conditions such as systemic lupus erythematosus [SLE]), single umbilical artery, fetal structural abnormalities, and hydrops fetalis. Most included studies were conducted in Turkey or Japan (Table 2).

FIGURE 4
Histopathologic features related to infectious/inflammatory/other



A, Acute chorioamnionitis in placenta from women with either T1DM or T2DM (n=642), GDM (n=250), T1DM (n=233), T2DM (n=288), and controls (n=77). **B**, Villitis of unknown etiology in placenta from women with either T1DM or T2DM (n=596), GDM (n=126), T1DM (n=264), T2DM (n=258), and controls (n=115). **C**, Fibrinoid necrosis in placenta from women with either T1DM or T2DM (n=105), GDM (n=2), T1DM (n=75), and controls (n=38). **D**, Villous edema in placenta from women with either T1DM or T2DM (n=340), GDM (n=2), T1DM (n=17), and mixed groups (n=42). **E**, Delayed villous maturation in placenta from women with either T1DM or T2DM (n=627), GDM (n=250), T1DM (n=174), T2DM (n=112), mixed groups (n=52), and controls (n=65)

GDM, gestational diabetes mellitus; *TIDM*, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

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Risk of bias of included studies. All the studies included in metaanalysis were given a rating of "good" by the authors at the conclusion of quality assessment; this suggests a uniformity across study methodology in all selected studies. A complete quality assessment is shown in Tables S4 and S5 (Supplementary Material).

Synthesis of results. The 14 included studies comprised a total of 478 "high-risk pregnancies" and 828 control or healthy pregnancies. Only 54 participants in the metaanalysis had GDM, and fewer than 10 participants had preexisting DM.

Placental stiffness was greater in women diagnosed with a variety of systemic maternal conditions (hypertensive disorders, IUGR, hyperglycemia, and autoimmune pathologies) than in healthy controls (mean difference 4.52 kPa [95% CI, 3.16−5.87]).

Placental stiffness was greater in pregnancies with fetal pathologies (mean difference was 6.5 kPa [95% CI, 1.08−11.86]) compared with control or healthy pregnancies.

Only 3 histopathologic studies after placental elastography were identified. Ohmaru et al[29] conducted in vivo placental elastography (reported in meter per second [m/s]) with histopathology, and their findings were included in our metaanalysis (Table 2 and Figures 6 and 7). Durhan et al[30] and Saw et al[31] conducted ex vivo placental elastography (reported in strain ratios). Consequently, these were not included in our metaanalysis. The histopathology of the placenta in all 3 of these elastography studies were similar to the changes described in key question 1.

Durhan et al[30] described increased syncytial knots, delayed villous maturation, villous fibrinoid necrosis and decidual vasculopathy, placental infarcts, (chronic) villitis, and chorioamnionitis. All of these were more common in the IUGR group than the control group (though depending on the region of placenta examined, the results were not always statistically significant). Saw et al[31] stained the placenta with specific stain "Verhoeff-Van Gieson" to evaluate the collagen and elastin contents. They found a high collagen:elastin ratio in high-risk pregnancies, but these histopathologic changes have not been described in association with diabetes specifically during pregnancy. Similarly, Ohmaru et al conducted special stains using Masson's trichrome to demonstrate increased collagen fibers.

Discussion

Main findings

Our main goal was to identify the role of SWE for detecting placental abnormalities in type 1 and type 2 DM using a systematic review and metaanalysis.

TABLE 1
Description of studies included in bar graph pictograms

Reference	Study population (N)	Control group (N)	Other study parameters
Starikov et al,[24] 2017	T1DM (117) and T2DM (176)	6 controls	Placental pathology compared with HbA1c groupings
Basnet et al,[38] 2016	T1DM and T2DM (76) mixed with GDM (130)	99 controls	
Huynh et al,[39] 2015	T1DM (36) and T2DM (37) mixed with GDM (126)	Nil	Two analyses were conducted. One of the analyses excluded women with preeclampsia, and the second included them.
Beauharnais et al,[40] 2012	T1DM (53) and T2DM (45)	Nil	
Tewari et al,[41] 2011	T1DM and T2DM (30)	30 controls	
Higgins et al,[42] 2011	T1DM and T2DM (74)	77 controls	
Evers et al,[43] 2003	T1DM and T2DM (58)	38 controls	Women with preeclampsia were excluded
Saldeen et al,[44] 2002	T2DM (2) mixed with GDM (9) and impaired glucose tolerance IGT (10)	10 controls	
Younes et al,[45] 1996	T1DM and T2DM (13) mixed with GDM (18)	17 controls	
Barth et al,[46] 1996	T1DM and T2DM (47)	Nil	
Honda et al,[47] 1992	T1DM and T2DM (21)	14 controls	
Clarson et al,[48] 1989	T1DM and T2DM (19)	11 controls	
Jacomo et al,[49] 1976	T1DM and T2DM (42)	20 controls	
Fox,[50] 1969	T1DM and T2DM (48)	234 controls	

TIDM, type 1 diabetes mellitus; *T2DM*, type 2 diabetes mellitus.

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We identified fewer than 10 participants meeting this population definition.

We found no placental histopathology features pathognomonic for DM. Although 16 placental features in women with preexisting DM are widely described, at least 1 study showed that similar findings were seen in women with fetal growth restriction.[30]

High placental stiffness scores have been shown in women with "high-risk pregnancies" such as hypertensive disorders and fetal growth restriction, but few studies included women with preexisting type 1 or type 2 DM. It is plausible that preexisting DM is another type of "high-risk" pregnancy leading to higher placental stiffness, but this is understudied to date.

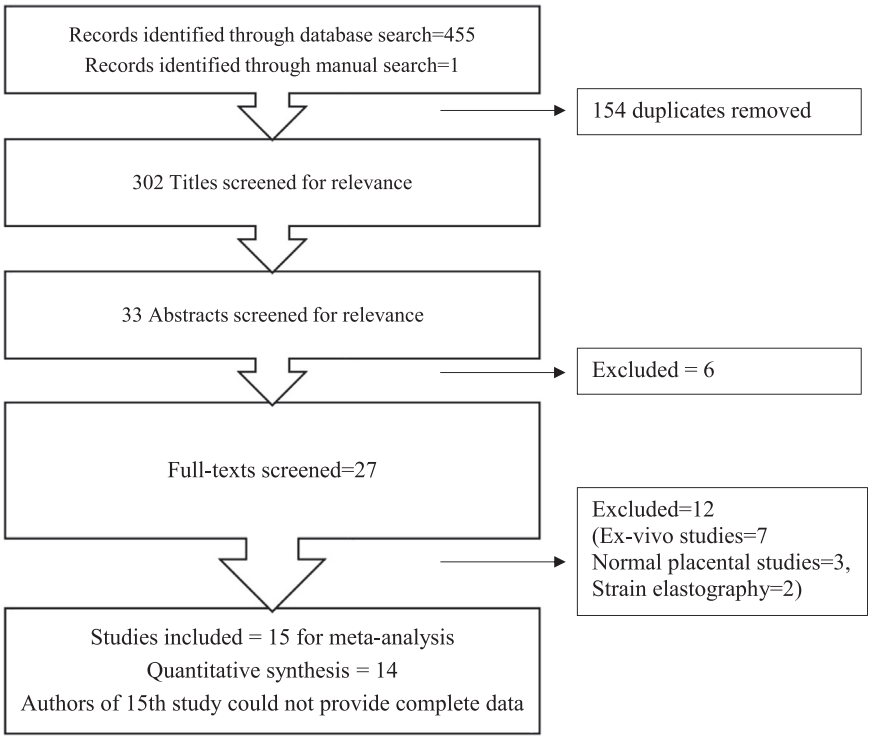
Interpretation (in light of other evidence)

For key question 1, regarding placental pathology in women with preexisting DM, our findings are consistent with a similar review by Huynh et al[32], though the inclusion and exclusion criteria differed. We excluded women with GDM, whereas Huynh et al[32] included this population. We included women with preeclampsia or hypertension associated with DM, whereas Huynh et al[32] excluded this group hoping to avoid the influence of "other pathologies." We acknowledge, however, that preexisting DM (and other chronic maternal vascular disease or autoimmune disease) are all accepted risk factors for the later development of preeclampsia.[14] Indeed, our literature review suggests that placental histopathology alone is unable to differentiate these maternal diseases. The placenta likely has a limited range of ways to respond to a multitude of insults. The result under the microscope may be similar despite differing underlying disease processes. Neither our review nor Huynh et al[32] reported placental disc weight as a histopathologic feature of DM. This is a macroscopic description worth noting in future studies.

For key question 2, with respect to the use of SWE in pregnancy, we intentionally excluded transient elastography and strain elastography in contrast to a previous Australian review on this topic.[33] We only included reports of stiffness in the form of m/s or kPa to enable metaanalysis. Our findings were similar to those of Edwards et al[33] that placental stiffness is higher in the setting of preeclampsia or other hypertensive disorders of pregnancy, fetal growth restriction, and maternal autoimmune disease.

For key question 1: it appears that type 1 and type 2 DM cause placental injury via similar pathways, with only 1 publication assessing their histopathology differences.[34] The same group investigated placental histopathology according to varying degrees of hyperglycemia. Using HbA1c as a marker[24], they found no significant placental

FIGURE 5
PRISMA flow diagram for the review (key question 2)



PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis. <FIGSE>*Gupta. Shear wave elastography and diabetes mellitus in pregnancy. Am J Obstet Gynecol MFM 2022.*

pathology differences with glucose in lower range (ie, <6.5%) vs higher range (ie, >8.5%). Another recent randomized controlled trial showed that metformin leads to reduced fetal growth in pregnancies affected by type 2 diabetes.[35] Further study is needed to explain this metformin effect on placental function and fetal growth.

For key question 2, considering placental stiffness measured in vivo, our systematic search identified fewer than 10 participants with preexisting DM for whom SWE values were available. We found no studies correlating histopathology findings with placental stiffness values (kPa or m/s) in women with preexisting diabetes. Such questions remain unanswered, indicating a need for further studies to fill gaps in the literature. We hypothesize that preexisting diabetes contributes to early "placental stress" (first trimester), but to date, SWE to detect this has not yet been studied.

A review of the mechanisms behind placental stress is beyond the scope of this review. However, some vascular components are worth noting. The "feto-placental unit" is the crucial link to maternal circulation, with both sides of this unit subject to hyperglycemia. Outside of pregnancy, maladaptive diabetic vascular processes[36] are well documented. These include a reduction of nitric oxide, higher levels of free radicals, raised production of endothelial vasoconstrictors such as COX-2, and finally, raised levels of free fatty acids. It is plausible that vascular dysfunction through these mechanisms and others may contribute toward "placental stress." Women with type 2 DM have an underlying insulin resistance and hypercoagulable state; pregnancy exacerbates both, potentially causing further ischemic stress to the fetoplacental unit.

Placental findings (elastography and histopathology) in women with hypertensive disorders of pregnancy or fetal growth restriction have been widely reported, but both these clinical syndromes become apparent quite late in gestation (second and third trimesters). Preexisting diabetes provides an opportunity to identify and/or intervene before clinical manifestations of "placental stress" may emerge. Doppler studies of fetal and maternal vessels can be measured in high-risk pregnancies, providing some clinical value for predicting adverse outcomes, but these have not been compared with SWE and could represent an opportunity for further investigation.

Strengths and limitations

Our search of placental histopathology occurrence in women with DM is summarized in bar graph format to demonstrate the most consistently reported features. There was significant heterogeneity in the histopathologic reporting methodologies, and in most reports, control group data were lacking. Many reports used specialized histopathology techniques, and we intentionally excluded these. Our bar graphs are developed from studies reporting only standard histopathology processing techniques, eg, hematoxylin and eosin staining of formalin-fixed, paraffin-embedded tissue. We believe this to be a strength of this study, as these techniques are most clinically relevant to a broad general surgical pathologist community. Another key strength of this review is the meta-analysis of in vivo placental elastography and stiffness scores in women with "high-risk" pregnancies. To the best of our knowledge, this is the first metaanalysis addressing this question.

The limitations of placental histopathology evaluation include the inherent subjective descriptions and arbitrary cut-offs contributing to positive findings. Underlying reporting bias is possible, ie, pathologists will identify features encountered in "traditional training." Delayed villous maturation, for example, may not be reported by general surgical pathologists, but specialist perinatal pathologists will identify it. We found that unique stains (Masson and Verhoeff-Van Gieson) were conducted in some studies to detect

TABLE 2
Characteristics of selected studies (N=15)

Condition	Author/year	Country	Gestational age (wk)	Method	Histopathology exam	N	
						Cases	Controls
DM (GDM+ODIP+PDM)	Ohmaru/2015	Japan	17–40[a]	VTTQ	Yes NP=12 DM=No	13	143
GDM	Bildaci/2017 (IADPSG criteria)	Turkey	24–28	ARFI	No	21	70
	Yuksel/2016 (CC criteria)	Turkey	30.5[a]	SWE	No	33	43
FGR/IUGR	Akbas/2019	Turkey		pSWE		66	81
	Habibi/2017	Turkey	25–33	SWE	No	42	42
	Ohmaru/2015	Japan	17–40[a]	VTTQ	Yes	21	143
PIH/ Gestational HTN/ Preeclampsia	Ohmaru/2015	Japan	17–40[a]	VTTQ	Yes	15	143
	Karaman/2016	Turkey	28–40	ARFI	No	34	38
	Alan/2016	Turkey	23–37	ARFI	No	42	44
	Cimsit/2015	Turkey	20–23	SWE	No	28	101
	Fujita/2019	Japan	16–32	pSWE	No	13	Low risk, no PE=181 High risk, no PE=27
	Karaman/2016	Turkey	28–40	ARFI	No	35	38
	Kilic/2015	Turkey	23–37	SWE	No	23	27
Placenta previa or placenta accreta	Alici Davutoglu/ 2018	Turkey	—	SWE	No	13 with acrreta, 13 without	43
Placental accreta spectrum	Cim/2018	Turkey	28–35	VTTQ	No	24	34
Collagen disease	Ohmaru/2015	Japan	17–40[a]	VTTQ	No	7	143
Single umbilical artery	Arslan/2019	Turkey	18–22	VTTQ	No	20	20
Fetal or structural anomalies	Alan/2016	Turkey	18–28[a]	ARFI	No	40	34
Hydrops fetalis	Cetin/2017	Turkey	Third trimester	ARFI	No	Rh-nonhydropic fetus=14 Rh-hydropic=16	28

ARFI, acoustic radiation force impulse; *CC criteria*, Carpenter and Coustan criteria; DM, diabetes mellitus; *FGR*, fetal growth restriction; *GDM*, gestational diabetes mellitus; *IUGR*, intrauterine growth restriction; *kPa*, kilopascal; *m/s*, meter per second; *NS*, nonsignificant; *PIH*, pregnancy-induced hypertension; *pSWE*, point shear wave elastography; *SWE*, shear wave elastography; *SWV*, shear wave velocity; *VTTQ*, virtual touch tissue quantification.

[a] No correlation between gestational age and SWV.

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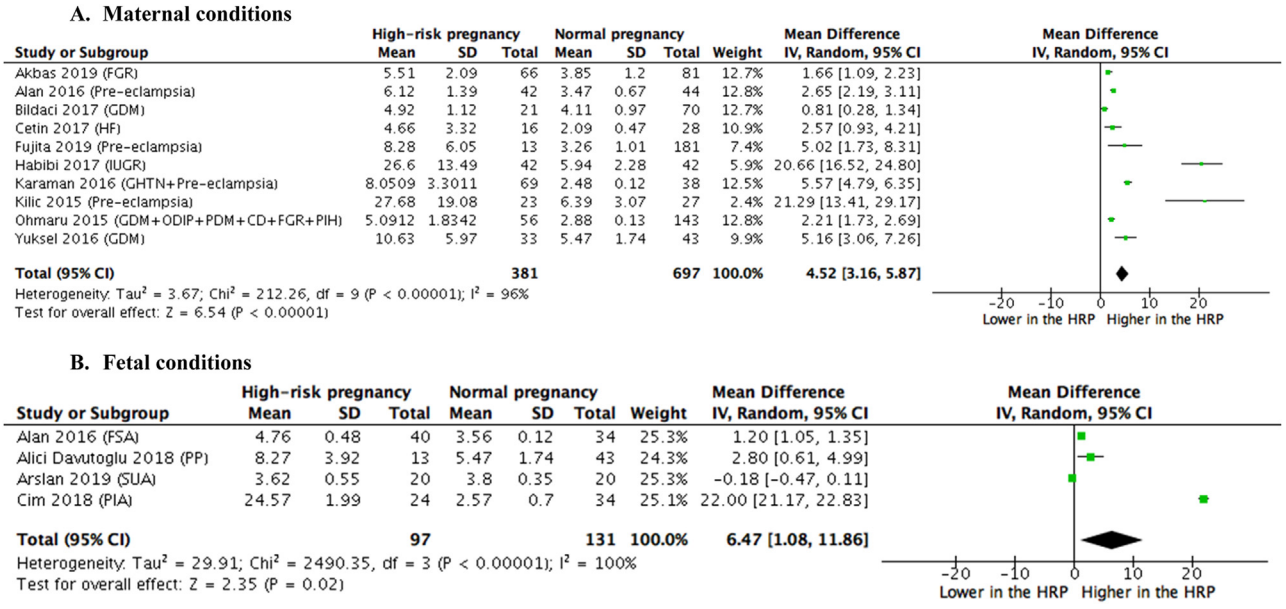
collagen, elastin, and fibrin. Examination of these stains by image analysis is not currently used in standard clinical practice. Increased automation in histopathology reporting may provide more objectivity in future research. Other specialized techniques using electron microscopy and immunohistochemistry are rarely used within standard clinical practice of placental reporting. We recognize that our exclusion of these specialized techniques might be considered a limitation, as the entirety of literature is not captured. International consortiums have attempted to develop global standards for placental pathology reporting. The Amsterdam International Statement[25] and "synoptic reporting" framework from Benton et al[37] will aid consistency in future research. Widespread adoption of these new reporting methodologies requires adjustment to training curricula, which is often a slow process.

Conclusions

There are no pathognomonic histopathology findings suggestive of DM in the placenta. Maternal conditions such as preeclampsia may demonstrate similar placental features under the microscope. Women with fetal growth restriction and hypertensive disorders have higher placental SWE stiffness. The current literature has not yet established placental SWE findings in women with DM. Further studies are

FIGURE 6 AND FIGURE 7

Forest plot comparing placental elasticity (shear wave velocity [kPa]) between normal and high-risk pregnancies



CD, collagen disease; *CI*, confidence interval; *FGR*, fetal growth restriction; *FSA*, fetal structural anomalies; *GDM*, gestational diabetes mellitus; *GHTN*, gestational hypertension; *HF*, hydrops fetalis; *HRP*, high-risk pregnancy; *IUGR*, intrauterine growth retardation; *IV*, weighted mean difference; *ODIP*, overt diabetes in pregnancy; *PDM*, preexisting diabetes mellitus; *PIA*, placenta accreta spectrum; *PIH*, pregnancy-induced hypertension; *PP*, placenta previa; *SD*, standard deviation; *SUA*, single umbilical artery.

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needed to investigate the effects of hyperglycemia and its treatment (insulin, metformin, and weight management) on placental structure, stiffness, and function. ■

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ajogmf.2022.100736.

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