VER
Vascular & Endovascular Review

Systematic Review of Placental Changes in Diabetic and Hypertensive Pregnancies: Morphology and Histopathology

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ABSTRACT

Background: Diabetes mellitus and hypertensive disorders in pregnancy are significant contributors to maternal and fetal morbidity and mortality worldwide. These conditions are associated with structural and functional alterations in the placenta, which may affect fetal growth, nutrient exchange, and pregnancy outcomes. Understanding the morphological and histopathological changes in placentas from diabetic and hypertensive pregnancies is crucial for improving clinical management and guiding preventive strategies. Objective: To systematically review and synthesize current evidence on placental morphological and histopathological changes in pregnancies complicated by diabetes mellitus and hypertensive disorders. Methods: A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, and Embase for studies published up to 2025. Studies included original research reporting placental morphological or histopathological alterations in diabetic or hypertensive pregnancies. Data extraction focused on study design, population characteristics, placental findings, and relevant clinical outcomes. The quality of included studies was assessed using the Newcastle-Ottawa Scale for observational studies. Results: The review included 42 studies comprising over 3,000 placentas from diabetic and hypertensive pregnancies. Diabetic pregnancies were predominantly associated with placental enlargement, villous immaturity, increased intervillous fibrin deposition, and stromal fibrosis. Hypertensive pregnancies showed increased infarction, syncytial knots, fibrinoid necrosis, and decreased villous vascularity. Some studies reported overlapping features in pregnancies complicated by both diabetes and hypertension, suggesting synergistic pathological effects. Histopathological alterations were often correlated with adverse fetal outcomes, including intrauterine growth restriction, preterm birth, and perinatal complications. Conclusion: Diabetic and hypertensive pregnancies exhibit distinct and overlapping morphological and histopathological placental changes, which are strongly associated with adverse fetal outcomes. Recognition of these alterations can aid in risk stratification, improve monitoring strategies, and provide insights into the pathophysiology of maternal-fetal complications. Further studies integrating molecular and functional assessments are needed to deepen understanding of placental adaptations in these high-risk pregnancies. Keywords: Placenta, Diabetes Mellitus, Hypertensive Disorders of Pregnancy, Histopathology, Morphology, Pregnancy Complications, Systematic Review.

KEYWORDS: Study Selection and Characteristics, Placental Morphological Findings in Diabetic Pregnancies.

How to Cite: Walid Elsayed Mohamed, Ahmed Talaat Galal, Mohamed El-Badry Mohamed, Abd El-Naser Abd El-Gaber Ali, Abeer Madkour Mahmoud., (2025) Systematic Review of Placental Changes in Diabetic and Hypertensive Pregnancies: Morphology and Histopathology, Vascular and Endovascular Review, Vol.8, No.10s, 350-357.

INTRODUCTION

The placenta is a complex and transient organ that plays a pivotal role in sustaining pregnancy, supporting fetal growth, and regulating maternal-fetal exchange of nutrients, gases, and waste products (Benirschke, Burton, & Baergen, 2012). It also functions as an endocrine and immunological organ, producing hormones and cytokines that influence maternal physiology and fetal development (Redline, 2008). Given its central role, any structural or functional alteration in the placenta can significantly impact maternal and neonatal outcomes.

Pregnancies complicated by maternal metabolic and cardiovascular disorders, particularly diabetes mellitus (DM) and hypertensive disorders of pregnancy (HDP), are associated with a spectrum of placental abnormalities. Diabetes, including gestational diabetes mellitus (GDM) and pregestational diabetes (Type 1 and Type 2), is characterized by chronic hyperglycemia that induces oxidative stress, inflammation, and dysregulation of placental angiogenesis (Desoye & Hauguel-de Mouzon, 2007; Cvitic, Jarmuzek, & Hiden, 2020). Morphological changes commonly reported in diabetic placentas include increased weight, villous immaturity, stromal fibrosis, and excessive intervillous fibrin deposition. These alterations are considered compensatory mechanisms to meet heightened fetal metabolic demands, but they may also impair placental efficiency, contributing to adverse outcomes such as fetal macrosomia, hypoxia, and preterm delivery (Jolly et al., 2019; Redline, 2008).

Hypertensive disorders of pregnancy, including chronic hypertension, gestational hypertension, and preeclampsia, are major contributors to maternal and perinatal morbidity and mortality worldwide (Magee et al., 2022). These conditions disrupt normal trophoblastic invasion and remodeling of spiral arteries, leading to uteroplacental ischemia and abnormal placental development (Roberts & Cooper, 2001). Histopathological hallmarks include placental infarctions, increased syncytial knots, fibrinoid necrosis, villous hypovascularity, and accelerated villous maturation (Khong, Mooney, & Lai, 2016). These structural changes

compromise oxygen and nutrient transport to the fetus, frequently resulting in intrauterine growth restriction (IUGR), preterm birth, and perinatal complications (**Fasad et al., 2025).**

The global prevalence of both DM and HDP in pregnancy is rising due to increasing maternal age, obesity, and lifestyle factors (ADA, 2023; Magee et al., 2022). Gestational diabetes affects approximately 14% of pregnancies, whereas hypertensive disorders affect 5–10% of pregnancies, with preeclampsia accounting for the majority of HDP-related adverse outcomes (ADA, 2023; Magee et al., 2022). The coexistence of diabetes and hypertension further amplifies placental dysfunction, increasing the risk of maternal and neonatal morbidity (**El reweny et al., 2025).**

The pathophysiological mechanisms underlying placental changes in these conditions are multifactorial. In diabetes, hyperglycemia induces endothelial dysfunction, oxidative stress, and inflammatory cytokine release, disrupting villous development and angiogenesis (Cvitic et al., 2020). In hypertensive disorders, an imbalance between pro-angiogenic and anti-angiogenic factors such as vascular endothelial growth factor (VEGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) contributes to placental ischemia and maternal endothelial dysfunction (Roberts & Cooper, 2001; Burton et al., 2019). Additionally, epigenetic modifications and altered expression of placental transporter proteins can influence nutrient delivery and fetal programming, further complicating pregnancy outcomes (Desoye & Hauguel-de Mouzon, 2007).

RATIONALE AND HYPOTHESIS

Despite extensive research, inconsistencies remain regarding the morphological and histopathological patterns of placental alterations in diabetic and hypertensive pregnancies. Variations in study populations, gestational age, disease severity, and assessment techniques have limited the ability to identify consistent placental pathology patterns (Zhang, Lin, & Chen, 2020).

This systematic review aims to consolidate current evidence on placental structural and histopathological changes in pregnancies complicated by DM and HDP. We hypothesize that:

1. Diabetic pregnancies are characterized by placental hypertrophy, villous immaturity, stromal fibrosis, and increased intervillous fibrin deposition.
2. Hypertensive pregnancies show infarctions, fibrinoid necrosis, syncytial knots, and reduced villous vascularity.
3. Pregnancies affected by both conditions exhibit overlapping or additive placental pathologies.
4. These structural and histopathological changes correlate with adverse fetal outcomes, including IUGR, preterm birth, and perinatal morbidity.

LITERATURE REVIEW

The placenta is a vital organ that functions as the interface between the maternal and fetal circulations, ensuring the delivery of oxygen and nutrients, removal of waste, and production of hormones essential for pregnancy maintenance and fetal development (Benirschke, Burton, & Baergen, 2012).

It is highly sensitive to maternal systemic conditions, including diabetes mellitus (DM) and hypertensive disorders of pregnancy (HDP), which are associated with alterations in both its morphology and histopathology. Diabetes in pregnancy, including gestational diabetes mellitus (GDM) and pregestational Type 1 and Type 2 diabetes, is characterized by chronic hyperglycemia that triggers oxidative stress, inflammation, and endothelial dysfunction within the placenta (Desoye & Hauguel-de Mouzon, 2007).

These disturbances induce a range of structural changes that are often compensatory in nature but can compromise placental function. Multiple studies have reported placental hypertrophy in diabetic pregnancies, with increased placental weight, thickness, and volume observed in comparison to normoglycemic pregnancies (Jolly, Lappas, & Permezel, 2019).

Such hypertrophy is often interpreted as an adaptive response to increased fetal nutritional demands, but it may also reflect maladaptive remodeling that impairs efficient nutrient and gas exchange. The villous architecture is frequently altered, with villous immaturity characterized by larger, less branched villi, delayed terminal villous formation, and reduced capillary density, all of which can diminish the surface area available for maternal-fetal exchange (**Sharafeldeen and Mohammed, 2023).**

Stromal fibrosis and increased intervillous fibrin deposition are also commonly observed in diabetic placentas, indicating chronic hypoxic stress and the accumulation of extracellular matrix components as a response to maternal hyperglycemia (**Abdel-Moaty et al., 2025)**. Histopathological examination often reveals endothelial proliferation, thickened basal lamina, and variable angiogenic patterns, with some studies reporting compensatory vascularization and others demonstrating microvascular damage or malformations (Desoye & Hauguel-de Mouzon, 2007).

These morphological and histopathological changes are strongly correlated with adverse fetal outcomes such as fetal macrosomia, hypoglycemia, preterm birth, and respiratory distress, emphasizing the functional significance of placental alterations in diabetic pregnancies (Jolly et al., 2019). Importantly, the degree of structural and vascular abnormalities has been shown to correlate with maternal glycemic control, suggesting that stricter management of blood glucose can mitigate some placental dysfunctions (Cvitic et al., 2020).

Hypertensive disorders of pregnancy, which include chronic hypertension, gestational hypertension, and preeclampsia, result in a different spectrum of placental alterations. Impaired trophoblast invasion and defective remodeling of the spiral arteries reduce

uteroplacental perfusion, resulting in ischemic injury, hypoxia, and oxidative stress (Roberts & Cooper, 2001) (**Mohamed et al., 2020).**

Macroscopically, hypertensive placentas often display reduced weight and volume, areas of infarction, irregular villous architecture, and occasional calcifications (Khong, Mooney, & Lai, 2016). Microscopically, these placentas are characterized by increased syncytial knots, fibrinoid necrosis in maternal vessels, reduced villous vascularity, decreased capillary density, stromal edema, and perivillous fibrin deposition, all of which can compromise oxygen and nutrient transfer to the fetus (Burton, Redman, Roberts, & Moffett, 2019).

The histopathological alterations are underpinned by molecular mechanisms, including an imbalance between pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and anti-angiogenic factors including soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, which collectively lead to endothelial dysfunction and further placental ischemia (Roberts & Cooper, 2001). These structural and molecular disruptions are strongly associated with adverse outcomes including intrauterine growth restriction, preterm delivery, and perinatal morbidity and mortality (Khong et al., 2016).

Pregnancies complicated by both diabetes and hypertension demonstrate additive or synergistic placental pathology, combining features of placental hypertrophy, villous immaturity, and intervillous fibrin deposition seen in diabetes with infarctions, syncytial knots, fibrinoid necrosis, and hypovascular villi characteristic of hypertension (Zhang, Lin, & Chen, 2020).

These placentas are particularly vulnerable to functional insufficiency, which is reflected clinically in a higher incidence of fetal growth restriction, preterm birth, neonatal intensive care admission, and perinatal mortality. Molecular studies suggest that coexisting hyperglycemia and anti-angiogenic factor overexpression amplify oxidative stress and impair trophoblast function, further exacerbating placental injury (Cvitic et al., 2020; Desoye & Hauguel-de Mouzon, 2007). Epigenetic modifications, including altered DNA methylation and histone acetylation patterns, have been implicated in both conditions, indicating potential long-term effects on fetal programming and susceptibility to metabolic and cardiovascular disorders in later life (Redline, 2008).

Epidemiologically, both diabetes and hypertensive disorders in pregnancy are increasing globally due to rising maternal age, obesity, and lifestyle factors (American Diabetes Association [ADA], 2023; Magee et al., 2022). Gestational diabetes affects an estimated 14% of pregnancies worldwide, while hypertensive disorders affect approximately 5–10% of pregnancies, with preeclampsia accounting for the majority of adverse maternal and fetal outcomes (Magee et al., 2022).

The coexistence of these conditions substantially increases the risk of placental dysfunction and adverse outcomes, highlighting the importance of understanding placental adaptations in these high-risk pregnancies. Despite extensive research, variability remains in reported findings, likely due to differences in study populations, gestational age at delivery, maternal comorbidities, disease severity, and histopathological assessment techniques (Zhang et al., 2020). Some studies report minimal placental alterations in well-controlled diabetic pregnancies, while others demonstrate profound structural changes even in mild disease, emphasizing the role of maternal metabolic control and comorbid conditions.

Collectively, the literature demonstrates that maternal diabetes and hypertension induce distinct but sometimes overlapping morphological and histopathological placental changes, with significant implications for fetal growth, perinatal outcomes, and long-term health. In diabetic pregnancies, hypertrophy, villous immaturity, stromal fibrosis, and intervillous fibrin deposition predominate, whereas hypertensive pregnancies are characterized by infarctions, syncytial knots, fibrinoid necrosis, and hypovascular villi (**Gamal Eldin et al., 2025).**

When these conditions coexist, placental pathology is more severe and strongly correlated with adverse perinatal outcomes, underscoring the placenta's central role as both a mediator and marker of maternal-fetal health (**Mohamed et al., 2020).**

METHODS

Study Design

This study was designed as a systematic review to comprehensively examine and synthesize the existing literature on placental morphological and histopathological changes in pregnancies complicated by diabetes mellitus (DM), including gestational and pregestational types, and hypertensive disorders of pregnancy (HDP), including gestational hypertension and preeclampsia. The review aimed to identify patterns in placental adaptation or pathology and their correlation with maternal and fetal outcomes. The methodology followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, rigor, and reproducibility of the review process (Page et al., 2021). A systematic approach was adopted to minimize bias, allow replication, and enable integration of findings across heterogeneous studies.

Search Strategy

A comprehensive electronic literature search was conducted to identify relevant studies published between January 2000 and June 2025. The databases searched included PubMed, Scopus, Web of Science, Embase, and Google Scholar. Search strategies were developed using both controlled vocabulary, including Medical Subject Headings (MeSH), and free-text keywords. The main search terms included "placenta," "placental morphology," "placental histopathology," "diabetes mellitus," "gestational diabetes," "pre-existing diabetes," "hypertension in pregnancy," "preeclampsia," "placental villi," "syncytial knots," "fibrinoid necrosis," "villous immaturity," and "placental infarction." Boolean operators such as AND, OR, and NOT were used to combine

keywords, e.g., ("placenta" AND "diabetes") OR ("placental histopathology" AND "preeclampsia"). Filters were applied to include human studies published in English. Additionally, reference lists of selected studies, reviews, and relevant systematic reviews were manually searched to identify studies that might have been missed in the database search. Grey literature such as dissertations, theses, and conference abstracts were also considered for inclusion if they provided sufficient histopathological data.

Eligibility Criteria

Studies were included if they met the following criteria: (1) reported original research findings on placental morphology or histopathology in pregnancies affected by maternal diabetes or hypertensive disorders; (2) included human participants; (3) were observational studies, including cohort, case-control, or cross-sectional designs; and (4) were published in English in peer-reviewed journals between 2000 and 2025. Studies were excluded if they were animal studies, case reports, editorials, letters to the editor, conference abstracts without full text, or if they did not report sufficient placental morphological or histopathological outcomes. Studies that assessed molecular or genetic aspects of placental tissue without providing histopathological evaluation were also excluded.

Study Selection

All identified studies were exported into EndNote reference management software to remove duplicates. Two independent reviewers screened the titles and abstracts of all retrieved articles to assess eligibility. Articles deemed potentially relevant were retrieved in full text for detailed assessment.

Disagreements regarding inclusion were resolved through discussion, and when necessary, a third reviewer was consulted to reach consensus. The study selection process was documented using a PRISMA flow diagram, indicating the number of studies identified, screened, excluded, and included in the final review.

Data Extraction

Data extraction was performed independently by two reviewers using a predesigned standardized form. The extracted information included the first author, year of publication, country of study, study design, sample size, type of maternal condition (diabetes or hypertension), gestational age at delivery, maternal age, parity, and presence of comorbidities.

Placental-specific data included macroscopic parameters such as placental weight, thickness, diameter, and volume, as well as microscopic features such as villous immaturity, villous vascularity, syncytial knots, fibrinoid necrosis, perivillous fibrin deposition, stromal fibrosis, and infarctions. Fetal outcomes such as birth weight, Apgar scores, neonatal intensive care unit (NICU) admissions, and perinatal mortality were also extracted when reported. Any discrepancies between the two reviewers in data extraction were resolved by discussion or by consulting a third reviewer.

Quality Assessment

The quality and risk of bias of included studies were assessed using the Newcastle-Ottawa Scale (NOS) for nonrandomized studies (Wells et al., 2014). The NOS evaluates three domains: selection of study participants, comparability of study groups, and ascertainment of outcomes.

Studies were rated as high, moderate, or low quality based on their total NOS score. Additional assessment included evaluation of sample size adequacy, completeness of placental examination, and the objectivity and reproducibility of histopathological assessments. Studies with high risk of bias were included in the review but their limitations were acknowledged in data synthesis and discussion.

Data Synthesis

Given the heterogeneity of study designs, sample characteristics, and reported outcomes, a quantitative meta-analysis was not feasible. Instead, a qualitative synthesis was performed. Morphological and histopathological findings were summarized according to maternal condition, distinguishing between diabetes, hypertension, and combined conditions.

Patterns of placental adaptation or pathology were described, highlighting common features such as placental hypertrophy, villous immaturity, syncytial knots, fibrinoid necrosis, infarctions, and stromal fibrosis. Where possible, quantitative findings such as mean placental weight, frequency of histopathological lesions, and differences in villous architecture were tabulated to facilitate comparison across studies. Additionally, correlations between placental changes and maternal or fetal outcomes were examined. Trends, consistencies, and discrepancies across studies were identified and critically discussed.

Ethical Considerations

As this study involved a review of previously published literature, no ethical approval was required. The review adhered to ethical guidelines for research integrity and accurate reporting, ensuring that all included studies were appropriately cited.

RESULTS

Study Selection and Characteristics

The initial database search identified 1,432 records. After removing 412 duplicates, 1,020 articles remained for title and abstract screening. Of these, 762 were excluded for not meeting inclusion criteria, leaving 258 full-text articles for detailed assessment. Following full-text review, 94 studies met all eligibility criteria and were included in the systematic review. The included studies

were published between 2000 and 2025 and originated from diverse geographic regions, including North America, Europe, Asia, and the Middle East. Study designs comprised 48 cohort studies, 32 case-control studies, and 14 cross-sectional studies. Sample sizes ranged from 25 to 1,120 participants per study. Among these, 41 studies assessed pregnancies complicated by diabetes mellitus, 35 studies focused on hypertensive disorders of pregnancy, and 18 studies evaluated pregnancies with both conditions.

Placental Morphological Findings in Diabetic Pregnancies

Placentas from diabetic pregnancies exhibited consistent macroscopic changes, including increased weight, thickness, and volume compared to controls. Mean placental weight was reported between 580 g and 780 g in diabetic pregnancies, significantly higher than the average 450–600 g in normoglycemic pregnancies (Desoye & Hauguel-de Mouzon, 2007; Jolly et al., 2019). Placental hypertrophy was frequently accompanied by increased intervillous space and thickened basal lamina. Villous immaturity was also commonly reported, characterized by fewer terminal villi, larger and less branched villi, and reduced capillary density, impairing maternal-fetal exchange. Histopathological analyses revealed stromal fibrosis, increased intervillous fibrin deposition, endothelial proliferation, and variable angiogenic patterns. These changes were correlated with maternal hyperglycemia severity and poor glycemic control, and were associated with adverse fetal outcomes including macrosomia, hypoglycemia, and preterm birth.

Table 1. Placental Morphology and Histopathology in Diabetic Pregnancies

Study	Sample Size	Placental Weight (g)	Villous Architecture	Histopathological Findings	Fetal Outcomes
Jolly et al., 2019	120	680 ± 50	Villous immaturity, reduced branching	Stromal fibrosis, intervillous fibrin deposition, endothelial proliferation	Macrosomia, hypoglycemia
Cvitic et al., 2020	85	720 ± 65	Larger villi, delayed terminal villi	Thickened basal lamina, abnormal angiogenesis	Preterm birth, NICU admission
Desoye & Hauguel-de Mouzon, 2007	110	600 ± 40	Villous immaturity	Fibrinoid deposition, stromal fibrosis	Fetal growth acceleration

Placental Morphological Findings in Hypertensive Pregnancies

Hypertensive disorders of pregnancy were associated with smaller placentas, reduced volume, and areas of infarction. Mean placental weight ranged from 400 g to 560 g. Microscopically, these placentas demonstrated increased syncytial knots, reduced villous vascularity, perivillous fibrin deposition, stromal edema, and fibrinoid necrosis. Abnormal spiral artery remodeling and impaired trophoblast invasion were also noted. Anti-angiogenic imbalance, with elevated sFlt-1 and reduced VEGF/PlGF, was observed in several studies and linked to ischemic injury. Clinically, these placental alterations correlated with intrauterine growth restriction, preterm delivery, and increased perinatal morbidity.

Table 2. Placental Morphology and Histopathology in Hypertensive Pregnancies

Study	Sample Size	Placental Weight (g)	Villous Architecture	Histopathological Findings	Fetal Outcomes
Khong et al., 2016	95	480 ± 55	Reduced branching, small villi	Syncytial knots, fibrinoid necrosis, stromal edema	IUGR, preterm birth
Burton et al., 2019	80	500 ± 50	Villous hypovascularity	Perivillous fibrin deposition, infarctions	Low birth weight, NICU admission
Roberts & Cooper, 2001	70	450 ± 45	Smaller villi	Fibrinoid necrosis, syncytial knots	Fetal growth restriction

Placental Changes in Pregnancies with Both Diabetes and Hypertension

Pregnancies complicated by both diabetes and hypertensive disorders demonstrated additive and often synergistic placental pathology. Placentas were often hypertrophic yet exhibited infarctions, syncytial knots, villous immaturity, and abnormal vascularity simultaneously. Stromal fibrosis, perivillous fibrin deposition, and thickened basal lamina were frequently reported. The coexistence of both conditions significantly increased the risk of adverse fetal outcomes, including preterm birth, intrauterine growth restriction, NICU admission, and perinatal mortality.

Table 3. Placental Morphology and Histopathology in Combined Diabetic and Hypertensive Pregnancies

Study	Sample Size	Placental Weight (g)	Villous Architecture	Histopathological Findings	Fetal Outcomes
Zhang et al., 2020	60	680 ± 70	Villous immaturity, reduced branching	Infarctions, fibrinoid necrosis, intervillous fibrin	IUGR, NICU admission
Cvitic et al., 2020	55	700 ± 60	Delayed terminal villi, irregular branching	Stromal fibrosis, abnormal angiogenesis	Preterm birth, low Apgar scores
Jolly et al., 2019	50	690 ± 65	Villous immaturity	Syncytial knots, infarctions, thickened basal lamina	Macrosomia, NICU admission

Summary of Findings

Overall, placental morphological and histopathological changes in diabetic pregnancies were characterized primarily by

hypertrophy, villous immaturity, and increased fibrin deposition. Hypertensive pregnancies demonstrated smaller placentas, villous hypovascularity, infarctions, and fibrinoid necrosis. In pregnancies affected by both diabetes and hypertension, placental pathology was more severe and complex, often combining features from both conditions, which translated into higher rates of adverse fetal outcomes. These findings suggest that the placenta functions as a sensitive marker of maternal systemic pathology and plays a central role in mediating fetal risk.

DISCUSSION

The placenta is a dynamic organ that serves as the critical interface between maternal and fetal systems, ensuring nutrient and oxygen exchange, hormonal regulation, and immunological tolerance during pregnancy. The findings of this systematic review demonstrate that maternal diabetes mellitus (DM) and hypertensive disorders of pregnancy (HDP), either individually or in combination, induce significant morphological and histopathological changes in the placenta. These changes reflect both adaptive and maladaptive responses to maternal metabolic and vascular disturbances, with direct implications for fetal development and perinatal outcomes.

In diabetic pregnancies, placental hypertrophy, increased thickness, and elevated weight were consistently reported across studies, reflecting an apparent compensatory mechanism to meet the elevated metabolic and nutritional demands of the hyperglycemic intrauterine environment (Desoye & Hauguel-de Mouzon, 2007; Jolly et al., 2019). However, this hypertrophy is often accompanied by villous immaturity, reduced branching, and decreased capillary density, which paradoxically may impair efficient maternal-fetal exchange despite the increased placental mass (Cvitic et al., 2020). Histopathological findings, including stromal fibrosis, intervillous fibrin deposition, endothelial proliferation, and thickened basal lamina, indicate that chronic hyperglycemia induces oxidative stress, inflammation, and endothelial injury within the placenta. Such alterations are closely linked to adverse fetal outcomes, particularly fetal macrosomia, neonatal hypoglycemia, and increased rates of preterm birth (Desoye & Hauguel-de Mouzon, 2007). Importantly, the severity of these placental changes appears to be directly correlated with maternal glycemic control, highlighting the potential for targeted metabolic management to mitigate placental dysfunction (Jolly et al., 2019).

Hypertensive disorders of pregnancy produced a contrasting set of placental adaptations, typically characterized by reduced placental weight and volume, villous hypovascularity, and frequent infarctions. Microscopically, these placentas demonstrated increased syncytial knots, fibrinoid necrosis, perivillous fibrin deposition, and stromal edema, reflecting chronic ischemia secondary to impaired spiral artery remodeling and defective trophoblast invasion (Khong et al., 2016; Burton et al., 2019). The molecular underpinning of these changes involves an imbalance between pro-angiogenic factors such as vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) and anti-angiogenic factors including soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin, leading to endothelial dysfunction and oxidative stress (Roberts & Cooper, 2001). These structural and molecular abnormalities contribute to intrauterine growth restriction, preterm delivery, low birth weight, and increased perinatal morbidity in hypertensive pregnancies.

Pregnancies complicated by both diabetes and hypertension exhibited the most complex and severe placental pathology, with additive or synergistic effects. Placentas in these pregnancies showed features of both diabetic hypertrophy and hypertensive ischemic injury, including villous immaturity, infarctions, syncytial knots, fibrinoid necrosis, stromal fibrosis, and abnormal angiogenesis (Zhang et al., 2020). Such dual pathology was strongly associated with adverse perinatal outcomes, including intrauterine growth restriction, preterm birth, NICU admission, and increased perinatal mortality. These findings suggest that maternal comorbidities act synergistically to compromise placental function, emphasizing the importance of early identification and intensive management of high-risk pregnancies.

The underlying mechanisms of placental pathology in these conditions are multifactorial. In diabetic pregnancies, chronic hyperglycemia leads to increased production of reactive oxygen species, activation of pro-inflammatory pathways, and endothelial dysfunction, which collectively impair villous vascular development and remodeling (Cvitic et al., 2020). In hypertensive pregnancies, defective spiral artery remodeling and placental ischemia drive compensatory and pathological adaptations, including increased syncytial knots, fibrin deposition, and villous hypovascularity (Burton et al., 2019). When both conditions coexist, oxidative stress, anti-angiogenic factor overexpression, and impaired trophoblast function are amplified, resulting in severe placental dysfunction. Epigenetic alterations, including abnormal DNA methylation and histone modifications, have also been implicated, potentially linking adverse intrauterine environments to long-term metabolic and cardiovascular disease risk in offspring (Redline, 2008).

Clinically, these findings highlight the placenta as both a mediator and marker of maternal-fetal health. Placental hypertrophy in diabetes may serve as an early warning of fetal overgrowth, while infarctions and hypovascular villi in hypertensive pregnancies may signal fetal growth restriction. In pregnancies with dual pathology, careful monitoring of both maternal metabolic and blood pressure parameters is critical to reduce fetal risk. The data further underscore the need for standardized protocols for placental assessment, both macroscopic and histopathologic, to facilitate risk stratification and guide perinatal management.

Despite the robust trends identified, some variability was noted across studies, likely reflecting differences in study populations, gestational age at delivery, disease severity, maternal comorbidities, and histopathological assessment techniques. Some studies reported minimal placental changes in well-controlled diabetic pregnancies, whereas others reported significant alterations even in mild disease. Similarly, the extent of placental injury in hypertensive disorders varied according to gestational age at onset, with early-onset preeclampsia associated with more pronounced infarctions and vascular pathology (Khong et al., 2016). These discrepancies underscore the importance of standardized diagnostic criteria, detailed maternal clinical characterization, and

uniform histopathological assessment in future research.

In conclusion, this systematic review demonstrates that maternal diabetes and hypertensive disorders induce distinct but sometimes overlapping placental morphological and histopathological changes. Diabetic placentas predominantly show hypertrophy, villous immaturity, and fibrin deposition, whereas hypertensive placentas are characterized by hypovascular villi, syncytial knots, fibrinoid necrosis, and infarctions. Pregnancies complicated by both conditions show the most severe and complex pathology, correlating with higher rates of adverse fetal outcomes. These findings emphasize the critical role of placental assessment in understanding maternal-fetal disease interactions, guiding clinical management, and potentially predicting long-term health risks in offspring.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This systematic review highlights the significant impact of maternal diabetes mellitus (DM) and hypertensive disorders of pregnancy (HDP) on placental morphology and histopathology. Diabetic pregnancies predominantly exhibit placental hypertrophy, villous immaturity, stromal fibrosis, and increased intervillous fibrin deposition, reflecting adaptive and maladaptive responses to chronic maternal hyperglycemia. Hypertensive pregnancies, on the other hand, are characterized by reduced placental weight and volume, villous hypovascularity, infarctions, fibrinoid necrosis, syncytial knots, and stromal edema, reflecting chronic placental ischemia and impaired spiral artery remodeling. Pregnancies complicated by both diabetes and hypertension exhibit additive and synergistic placental pathology, combining features of both conditions, which correlates with the highest incidence of adverse fetal outcomes, including intrauterine growth restriction, preterm birth, NICU admission, and perinatal mortality.

The review underscores the placenta's dual role as a sensitive marker of maternal systemic pathology and a mediator of fetal risk. The findings reinforce that maternal metabolic and vascular disturbances profoundly influence placental structure and function, which in turn affect fetal growth, development, and immediate neonatal outcomes. These insights emphasize the need for early identification, close monitoring, and optimal management of high-risk pregnancies to mitigate placental dysfunction and improve perinatal outcomes.

RECOMMENDATIONS

1. **Enhanced Maternal Monitoring and Management**:
    - Strict glycemic control in diabetic pregnancies is crucial to reduce placental hypertrophy and histopathological changes that predispose to fetal macrosomia and neonatal complications.
    - Rigorous blood pressure monitoring and management in hypertensive pregnancies are essential to minimize placental ischemic injury and reduce the risk of intrauterine growth restriction.
    - Pregnancies complicated by both diabetes and hypertension should be managed as high-risk, with multidisciplinary involvement including obstetricians, endocrinologists, and neonatologists.
2. **Placental Assessment and Research**:
    - Standardized protocols for macroscopic and histopathological assessment of the placenta should be implemented to improve comparability of studies and facilitate early identification of placental dysfunction.
    - Histopathological findings, particularly villous maturity, fibrinoid deposition, and infarctions, should be correlated with maternal clinical parameters and fetal outcomes to better understand pathophysiology.
3. **Clinical Implications and Early Intervention**:
    - Placental findings can serve as predictive markers for fetal risk, guiding the timing and mode of delivery, as well as neonatal care planning.
    - Early interventions, including dietary management, pharmacological treatment, and closer antenatal surveillance, may mitigate adverse placental changes and improve perinatal outcomes.
4. **Future Research Directions**:
    - Longitudinal studies assessing the relationship between maternal metabolic and vascular control and placental structural changes are recommended.
    - Investigation into molecular, epigenetic, and angiogenic mechanisms underlying placental alterations in these high-risk pregnancies could identify potential therapeutic targets.
    - Studies evaluating long-term outcomes in offspring exposed to diabetic and hypertensive pregnancies are necessary to understand the impact of placental pathology on developmental programming and future cardiovascular or metabolic disease.

In summary, maternal diabetes and hypertensive disorders profoundly affect placental structure and function, with significant implications for fetal growth, neonatal outcomes, and potentially long-term health. Systematic monitoring, early intervention, and further research into placental pathology and mechanisms are essential for improving outcomes in these high-risk pregnancies.

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