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Maternal Diabesity and Fetoplacental Dysfunction: Pathophysiological Pathways and Clinical Implications

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Abstract

Background. Maternal diabesity, defined as the coexistence of obesity and diabetes during pregnancy, is an increasingly prevalent metabolic condition associated with adverse maternal, placental, and fetal outcomes. Beyond hyperglycemia, it is characterized by chronic inflammation, insulin resistance, oxidative stress, endothelial dysfunction, which impair placental development and function. The fetoplacental unit represents a critical interface through which maternal metabolic disturbances shape fetal growth and long-term health.

Aim. To integrate current evidence on placental diabesity, focusing on key mechanisms linking maternal metabolic dysfunction to placental maladaptation and its clinical implications for pregnancy and offspring outcomes.

Material and methods. This research was based on a literature review of PubMed and Web of Science articles published between 2010-2025. Peer-reviewed experimental, clinical and translational studies, meta-analyses were included and synthesized narratively.

Description of knowledge. The available evidence indicates that maternal diabesity induces early and persistent fetoplacental dysfunction, characterized by impaired endothelial insulin signaling, reduced nitric oxide bioavailability, enhanced oxidative and inflammatory stress, mitochondrial impairment, and activation of endoplasmic reticulum stress pathways. These interconnected alterations compromise placental blood flow, nutrient transport, and metabolic adaptability, thereby increasing fetal exposure to an adverse intrauterine environment and contributing to developmental programming of metabolic and cardiovascular disease.

Conclusions. Fetoplacental dysfunction is a key mechanism linking maternal diabesity to impaired fetal development and long-term offspring health. Understanding placental maladaptation in diabesity is essential for developing preventive and therapeutic strategies beyond glycaemic control to reduce intergenerational metabolic risk.

Keywords: placental diabesity, maternal obesity, gestational diabetes mellitus, placental dysfunction, fetal programming, metabolic disease

Content

Abstract 2

Keywords 2

1. Introduction 4

2. Aim of the study 5

3. Material and methods 5

3.1. Literature search strategy 5

3.2. Study selection process 6

3.3. Data extraction and synthesis 6

4. Description of knowledge 7

4.1. Placental structural and functional adaptations in maternal diabesity 7

4.2. Placental mitochondrial and endoplasmic reticulum dysfunction in gestational diabesity 8

4.3. Placental inflammation and immune dysregulation 9

4.4. Fetoplacental endothelial dysfunction and fetal vascular insulin resistance in gestational diabesity 10

4.5. Short- and long-term fetal and offspring complications of gestational diabesity 12

5. Limitations 13

6. Conclusions 14

Disclosures 14

Author Contributions 14

Funding 14

Institutional Review Board Statement 14

Informed Consent Statement 14

Data Availability Statement 14

Conflicts of Interest 14

References 15

1. Introduction

The global rise in obesity and diabetes represents one of the most pressing contemporary public health challenges. According to a comprehensive analysis from the Global Burden of Disease Study 2021, adult overweight and obesity affected over 1.00 billion males and 1.11 billion females in 2021, while approximately 537 million people were living with diabetes globally, with the prevalence continuing to increase across all age groups [1,2]. During pregnancy, maternal overweight/obesity increases the risk of developing gestational diabetes mellitus (GDM) by 2-4-fold compared with lean women [3,4]. This shared metabolic and inflammatory pathology underlies the coexistence of obesity and diabetes, giving rise to gestational diabesity, a dysmetabolic state characterized by insulin resistance, chronic low-grade inflammation, oxidative stress, and endothelial dysfunction [5,6]. Of particular concern is the growing prevalence of diabesity among women of reproductive age, where obesity rates exceed 30–40% in many populations and GDM affects approximately 5–20% of pregnancies worldwide, depending on diagnostic criteria and ethnicity [7–9]. Consequently, an increasing proportion of pregnancies are complicated by the concurrence of pre-pregnancy obesity and GDM, a condition commonly referred to as gestational diabesity.

Pregnancy represents a unique physiological state in which profound maternal metabolic adaptations are required to support fetal growth and development. The placenta plays a central role in this process, acting as a highly specialized and metabolically active organ that regulates nutrient transport, gas exchange, endocrine signaling, immune tolerance, and vascular adaptation between mother and fetus [10,11]. Exposure to a diabetogenic maternal environment disrupts these tightly regulated processes. Maternal hyperglycemia, hyperinsulinemia, dyslipidemia, and inflammatory mediators converge at the fetoplacental interface, triggering maladaptive placental responses that impair vascular reactivity, mitochondrial function, and cellular homeostasis [9,12].

Fetoplacental dysfunction is a key pathophysiological feature of pregnancies complicated by GDM and maternal obesity, initially driven by impaired endothelial insulin signaling and reduced nitric oxide bioavailability, which disturb the balance between vasodilator and vasoconstrictor pathways and compromise placental perfusion and nutrient delivery [7,13]. In gestational diabesity, the coexistence of obesity and diabetes further amplifies inflammatory signaling within the placental microenvironment, promoting mitochondrial dysfunction characterized by impaired oxidative capacity and increased mitochondrial-derived reactive oxygen species, which in turn exacerbate oxidative stress and endothelial impairment [11,14]. These mitochondrial alterations interact with endoplasmic reticulum stress pathways, reinforcing insulin resistance and inflammatory responses in fetoplacental tissues and contributing to early placental maladaptation, with disrupted growth and vascular programming detectable from the first trimester onward [10,15,16].

The consequences of fetoplacental dysfunction extend well beyond pregnancy. Epidemiological and experimental studies support the concept of developmental programming, whereby exposure to a diabetogenic intrauterine environment increases the risk of abnormal fetal growth, neonatal hyperinsulinemia and adiposity, and long-term susceptibility to childhood obesity, insulin resistance, type 2 diabetes, and cardiovascular diseases [17,18]. These effects are mediated by persistent alterations in vascular, metabolic, and epigenetic regulation across multiple tissues, underscoring the critical importance of the intrauterine environment in shaping lifelong health trajectories [6,19]. In this context, a comprehensive understanding of the mechanisms linking maternal diabesity to fetoplacental dysfunction is essential.

2. Aim of the study

This narrative review aims to provide an integrative overview of placental diabesity, focusing on the molecular, cellular, and vascular mechanisms by which maternal metabolic dysfunction drives placental maladaptation and adverse fetal outcomes. Furthermore, we discuss the clinical implications of these pathways for pregnancy outcomes and long-term offspring health to inform future preventive and therapeutic strategies.

3. Material and methods

3.1. Literature search strategy

This narrative review was conducted using a structured literature search in the PubMed and Web of Science databases, covering the period from January 1, 2010, to December 14, 2025. The search strategy included combinations of the following key terms and their synonyms: maternal obesity, gestational diabetes mellitus, gestational diabesity, placental dysfunction, fetoplacental unit, endothelial dysfunction, insulin signaling, oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, fetal programming, and offspring metabolic disease. Medical Subject Headings (MeSH) terms were applied when appropriate to improve search precision. Reference lists of relevant original articles and review papers were manually screened to identify additional eligible studies.

Table 1. Inclusion and exclusion criteria applied for study selection in the narrative review of maternal diabesity and fetoplacental dysfunction.

Inclusion Criteria	Exclusion Criteria
Peer-reviewed articles published in English	Case reports, conference abstracts, letters without substantial original data, and non-peer-reviewed publications
Human studies, translational research or high-quality mechanistic studies relevant to maternal diabesity and placental function	Studies focusing exclusively on maternal or fetal outcomes without assessment of placental structure or function
Systematic reviews, meta-analyses, randomized controlled trials, observational studies, and narrative reviews	Animal-only studies unless they provided mechanistic insights with clear translational relevance to human pregnancy
	Publications outside the predefined time window

3.2. Study selection process

After removal of duplicate records, titles and abstracts were screened for relevance to the scope of the review. Full-text articles were subsequently assessed to confirm eligibility according to the predefined inclusion and exclusion criteria. From the initial search output, a selected body of key publications was retained for final synthesis, including systematic reviews, meta-analyses, clinical studies, observational cohorts, and translational research articles addressing maternal diabesity and fetoplacental dysfunction.

3.3. Data extraction and synthesis

Extracted data included study design, population characteristics, maternal metabolic status, placental structural and functional alterations, vascular and endothelial signaling pathways, mitochondrial and endoplasmic reticulum stress markers, inflammatory and oxidative stress profiles, and reported fetal or offspring outcomes. Owing to the heterogeneity in study design, methodologies, and outcome measures, a qualitative narrative synthesis was performed. Findings were organized thematically, with dedicated sections focusing on placental vascular dysfunction, metabolic and

mitochondrial impairment, cellular stress responses, and their implications for fetal programming and long-term offspring health.

4. Description of knowledge

4.1. Placental structural and functional adaptations in maternal diabesity

Maternal diabesity, encompassing both obesity and GDM, induces profound alterations in placental structure and function that compromise fetoplacental efficiency. Evidence consistently demonstrates that obesity and GDM, independently and synergistically, are associated with placental overgrowth characterized by increased placental weight, thickness, and volume [20–22]. Importantly, this enlargement is frequently accompanied by a reduced fetal-to-placental weight ratio, indicating diminished placental efficiency rather than enhanced exchange capacity [21].

Quantitative clinical data support the functional relevance of these structural changes. In term pregnancies delivered by elective cesarean section, placentas from obese women were significantly heavier and thicker than those from normal-weight controls, while fetuses—particularly in pregnancies complicated by GDM—exhibited lower umbilical oxygen saturation and increased acidosis [21]. These findings suggest that placental hypertrophy in maternal diabesity may represent a compensatory response to an adverse metabolic environment that ultimately fails to preserve adequate fetal oxygenation [21].

Placental vascular dysfunction represents a central mechanism underlying reduced exchange efficiency. Histological and imaging studies in GDM pregnancies consistently report villous immaturity, abnormal branching, and vascular lesions, changes that likely increase diffusion distance and impair perfusion [22]. Three-dimensional ultrasound analyses further demonstrate that placental volume is increased in both obese and GDM pregnancies, whereas vascularization indices are significantly reduced, particularly in GDM [23]. These observations indicate a dissociation between placental growth and vascular development, predisposing the fetus to relative hypoxia.

At the molecular level, maternal diabesity is associated with dysregulation of angiogenic, inflammatory, and endocrine pathways. Reduced placental vascular endothelial growth factor (VEGF) and leptin concentrations have been reported in obese and GDM pregnancies and correlate with impaired placental vascularization [23]. In parallel, obesity-related low-grade inflammation alters placental cytokine profiles, with increased tumor necrosis factor α (TNF-α) immunostaining and disrupted interleukin 6 (IL-6) distribution, changes that may interfere with insulin signaling and nutrient transport [20]. Such inflammatory adaptations may further exacerbate placental inefficiency and fetal metabolic stress.

Beyond glucose handling, placental lipid transport is markedly affected by maternal diabesity. Obesity and GDM alter placental fatty acid composition and the expression of key transporters, including fatty acid transport protein (FATP) 1, 4, 6, and FAT/CD36, independently of total placental lipid content [24]. These changes are accompanied by shifts in placental phospholipid species, with increased arachidonic and docosahexaenoic acid and reduced dihomo-γ-linolenic acid, which correlate with placental weight and fetal fatty acid status. Such alterations may contribute to abnormal fetal growth patterns and long-term metabolic programming [25].

Emerging evidence also implicates epigenetic mechanisms in placental adaptation to maternal diabesity. Increased global DNA methylation has been observed in placentas from obese and GDM pregnancies, with more pronounced effects in GDM, suggesting stable reprogramming of genes involved in angiogenesis, inflammation, and nutrient transport [23].

4.2. Placental mitochondrial and endoplasmic reticulum dysfunction in gestational diabesity

Gestational diabesity alters the maternal metabolic and hormonal milieu already in early pregnancy, a period when placental growth and differentiation are highly sensitive to oxidative and inflammatory signals [15]. Evidence from first-trimester human placentas demonstrates that exposure to diabesity is associated with increased oxidative and inflammatory stress signaling at a stage critical for trophoblast proliferation, fusion and placental surface expansion, potentially predisposing the placenta to later functional impairment [15]. This early susceptibility provides a mechanistic framework linking gestational diabesity to persistent placental organelle stress.

Mitochondrial dysfunction is a consistent feature of placentas from pregnancies complicated by obesity and diabetes. Studies of term placentas show reduced oxygen consumption rates, decreased ATP production and downregulation of electron transport chain complexes, particularly complex I, together with increased mitochondrial reactive oxygen species generation [26–28]. These bioenergetic defects are modest in obesity alone but are exacerbated when obesity coexists with gestational diabetes, indicating limited adaptive capacity of placental mitochondria under combined metabolic stress [11,27]. Although compensatory increases in mitochondrial biogenesis have been reported in obese normoglycemic pregnancies, this response is attenuated in gestational diabesity and accompanied by structural mitochondrial abnormalities, suggesting impaired mitochondrial quality and function [28].

Disruption of mitochondrial dynamics and clearance further contributes to placental dysfunction [29]. Altered expression of proteins regulating fusion, fission and mitophagy has been described in placentas from obese and GDM pregnancies, with incomplete activation of mitophagy leading to the accumulation of dysfunctional mitochondria within trophoblast cells. These defects

are associated with reduced mitochondrial respiratory capacity and increased oxidative stress, reinforcing a vicious cycle of organelle damage [29].

Endoplasmic reticulum (ER) stress represents a convergent and interacting pathway in placental pathology associated with gestational diabesity. Activation of unfolded protein response signaling, including increased phosphorylation of inositol-requiring enzyme 1 alpha (IRE1α, a key endoplasmic reticulum stress sensor) and upregulation of CCAAT/enhancer-binding protein homologous protein (CHOP, a key ER stress–induced pro-apoptotic factor), has been demonstrated in fetoplacental tissues exposed to obesity and GDM [16]. Importantly, recent data show that obesity concurrent with GDM induces maladaptive remodeling of mitochondria–ER contact sites, enhancing calcium transfer, oxidative stress and trophoblast apoptosis [30]. Collectively, mitochondrial dysfunction and ER stress form an integrated pathological axis that compromises placental efficiency and likely contributes to fetal complications.

4.3. Placental inflammation and immune dysregulation

Placental inflammation is a reproducible feature of pregnancies complicated by the coexistence of obesity and GDM [31]. Obesity is associated with chronic low-grade inflammation, which extends to the placenta and is reflected by altered expression of pro-inflammatory cytokines, particularly TNF-α and IL-6 [20]. In a human cohort study, syncytiotrophoblast TNF-α immunostaining was significantly increased in placentas from obese women, whereas IL-6 localization within placental stroma and fetal vessels was modified in a manner partly dependent on GDM status [20]. Importantly, maternal circulating TNF-α concentrations were reduced in GDM pregnancies, indicating that inflammatory regulation in combined metabolic disease is tissue-specific and not necessarily mirrored at the systemic level [20].

Immune-focused analyses further support the presence of subclinical placental and systemic immune activation. Distinct immune signatures were observed depending on maternal adiposity [32]. Obese women with GDM exhibited elevated circulating IL-6 and IL-17A, whereas non-obese women with GDM showed increased placental IL-17A expression and enhanced interferon-γ production in visceral adipose tissue [32]. Unsupervised clustering approaches identified an expansion of tissue monocyte populations specifically in obese GDM pregnancies, linking increased adiposity with heightened innate immune activation at the maternal–fetal interface [32].

At the molecular level, altered adenosine metabolism and signaling may modulate placental inflammatory responses. Elevated extracellular adenosine concentrations and increased expression of A2B adenosine receptors have been reported in placental tissues from GDM and obese pregnancies, correlating with hyperglycemia and oxidative stress [14]. Activation of A2B receptors is associated with anti-inflammatory signaling under high-adenosine conditions, suggesting a

compensatory mechanism aimed at restraining excessive placental inflammation [14]. Whether this pathway remains protective or becomes insufficient under sustained metabolic stress remains to be clarified.

4.4. Fetoplacental endothelial dysfunction and fetal vascular insulin resistance in gestational diabesity

The fetoplacental endothelium constitutes a key regulatory interface between maternal metabolic adaptations to pregnancy and fetal perfusion. Endothelial dysfunction—defined as an imbalance between vasodilatory and vasoconstrictive mediators produced by or acting on endothelial cells—is closely linked to altered vascular insulin responses [7,9,12,33]. In pregnancy, a degree of physiological insulin resistance normally develops to ensure adequate glucose availability for the growing fetus. However, when pregnancy occurs in women with pre-pregnancy overweight or obesity who subsequently develop GDM, this adaptive mechanism is exposed to sustained hyperglycemia, hyperinsulinemia, and/or dyslipidemia, resulting in maladaptive fetoplacental endothelial signaling and fetal vascular insulin resistance [7,13,34].

4.4.1. Altered L-arginine/NO pathway

A central hallmark of fetoplacental endothelial dysfunction in gestational diabesity is dysregulation of the L-arginine/nitric oxide (NO) pathway. In human umbilical vein and placental microvascular endothelial cells (HUVEC and hPMEC) from GDM pregnancies, increased expression and activity of the human cationic amino acid transporter (hCAT-1) leads to enhanced L-arginine uptake and elevated endothelial NO synthase (eNOS) activity [33–35]. This paradoxical increase in NO production does not translate into improved vasodilation, reflecting a state of NO signaling uncoupling. Experimental studies using primary HUVEC and hPMEC cultures demonstrate that despite increased eNOS expression, insulin-mediated vasodilation is blunted, and relaxation of umbilical vein rings in response to insulin or calcitonin gene-related peptide is impaired [7,35].

These findings indicate that chronic metabolic stress shifts NO signaling from a tightly regulated vasoprotective mechanism to a maladaptive response characterized by altered downstream signaling, increased oxidative/nitrative stress, and reduced vascular responsiveness. Importantly, such alterations persist even in diet-controlled or insulin-treated GDM pregnancies in which maternal and neonatal glycaemia are normalized at term, underscoring that endothelial dysfunction is not merely a consequence of hyperglycemia but reflects deeper metabolic imprinting of the fetoplacental vasculature [7,35,36].

4.4.2. Dysregulated insulin–adenosine axis

The insulin–adenosine axis represents a critical regulatory system linking metabolic and vascular signaling in the fetoplacental endothelium. In normal pregnancy, insulin promotes vasodilation partly by reducing adenosine uptake through equilibrative nucleoside transporters (hENT1 and hENT2), thereby increasing extracellular adenosine availability and activating A_2A adenosine receptors (A_2AAR) [37,38]. Activation of A_2AAR is required for insulin-stimulated L-arginine transport and NO synthesis in human placental endothelial cells [37].

In GDM, adenosine handling is profoundly altered. Human studies demonstrate increased adenosine concentrations in umbilical vein blood—but not in umbilical arteries—indicating impaired endothelial uptake rather than increased placental production [38,39]. This phenomenon is linked to reduced expression and activity of hENT1 in macrovascular endothelium and hENT2 in microvascular endothelial cells [33,38,39]. Although insulin can restore hENT expression and adenosine transport in vitro, this effect critically depends on intact insulin receptor signaling, particularly balanced expression of insulin receptor isoforms A and B [33,39].

Under physiological conditions, insulin modulates adenosine transport and endothelial NO synthesis via phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)-dependent signaling, partly depending on the balance between insulin receptor isoforms (IR-A and IR-B) [13,35]. In gestational diabesity, however, endothelial insulin responsiveness is impaired, limiting insulin's ability to normalize adenosine handling and vascular tone despite hyperinsulinemia. This fetal vascular insulin resistance may compromise fine regulation of fetoplacental blood flow and nutrient delivery, contributing to abnormal fetal growth trajectories [39].

4.4.3. Intracellular alkalinization and endothelial dysfunction

An additional, often overlooked component of fetoplacental endothelial dysfunction in diabetic pregnancies is altered intracellular and extracellular pH regulation [7,9,40]. Human placental studies demonstrate increased expression and activity of the Na^+/H^+ exchanger (NHE1) in endothelial and trophoblast cells from diabetic pregnancies, resulting in intracellular alkalinization and extracellular acidification [7,40]. Elevated intracellular pH modulates insulin signaling, transporter activity, and enzyme function, including eNOS coupling and adenosine transport [7,40]. These pH-dependent changes may further exacerbate endothelial insulin resistance and impair vascular reactivity within the fetoplacental unit.

4.4.4. Therapeutic considerations and vascular dysfunction

While insulin therapy is essential for achieving maternal glycemic control in GDM, evidence from human studies indicates that maternal insulin treatment alone does not fully restore fetoplacental endothelial function [36,37]. Endothelial cells from insulin-treated GDM pregnancies

continue to exhibit increased hCAT-1 expression, altered NO signaling, impaired vasodilation, and persistent insulin resistance. These findings highlight the need for adjunctive therapeutic strategies targeting endothelial signaling pathways, including modulation of adenosine receptors, restoration of balanced IR-A/IR-B signaling, and correction of metabolic microenvironmental factors such as pH and lipid disturbances.

Collectively, these data support the concept that gestational diabesity induces a complex, interconnected network of fetoplacental endothelial alterations involving the L-arginine/NO pathway, insulin–adenosine signaling, intracellular pH regulation, and selective vascular insulin resistance. These mechanisms persist beyond normalization of glycemia and likely contribute to both immediate fetal vascular dysfunction and long-term metabolic programming.

4.5. Short- and long-term fetal and offspring complications of gestational diabesity

As described above, gestational diabesity impairs placental development and function, leading to altered nutrient transport and endocrine signaling that underlie many fetal and offspring complications [8]. In the short term, gestational diabesity is strongly associated with fetal overgrowth, macrosomia, and increased neonatal adiposity, reflecting excessive transplacental glucose and lipid transfer. Neonates are at increased risk of hypoglycemia, hyperinsulinemia, respiratory morbidity, and neonatal intensive care unit admission [8]. Large cohort studies further show higher rates of preterm birth, low Apgar scores, and perinatal morbidity in pregnancies complicated by maternal obesity and GDM, with their coexistence amplifying selected adverse outcomes, including stillbirth and hypertensive complications [12,41,42].

Long-term consequences extend well beyond the perinatal period and predominantly affect metabolic health. Offspring exposed to gestational diabesity display increased risk of childhood and adult obesity, insulin resistance, impaired glucose tolerance, and type 2 diabetes. Epidemiological data indicate that offspring of obese mothers have up to a threefold higher risk of developing obesity later in life, while in utero exposure to GDM is associated with a significantly increased risk of dysglycemia and metabolic syndrome across the life course [8,12]. These outcomes are consistent with permanent alterations in adipose tissue development, appetite regulation, and insulin signaling established during fetal life.

Cardiovascular involvement constitutes an important component of this broader cardiometabolic programming. Fetoplacental endothelial dysfunction in gestational diabesity is associated with altered fetal hemodynamics and early cardiac remodeling, including ventricular hypertrophy and impaired myocardial performance detectable in utero and infancy. Follow-up studies suggest increased vascular stiffness and higher blood pressure in exposed offspring, supporting an elevated long-term cardiovascular risk embedded within the metabolic phenotype [8,12].

At the mechanistic level, many of these short- and long-term effects are mediated by epigenetic remodeling. Maternal hyperglycemia and obesity induce persistent changes in DNA methylation, histone modifications, and non-coding RNA expression in placental tissue and fetal organs, affecting pathways involved in growth, metabolism, inflammation, and organ development. Experimental evidence further suggests that these programmed effects may extend across generations, emphasizing the lasting biological impact of gestational diabesity [12,17].

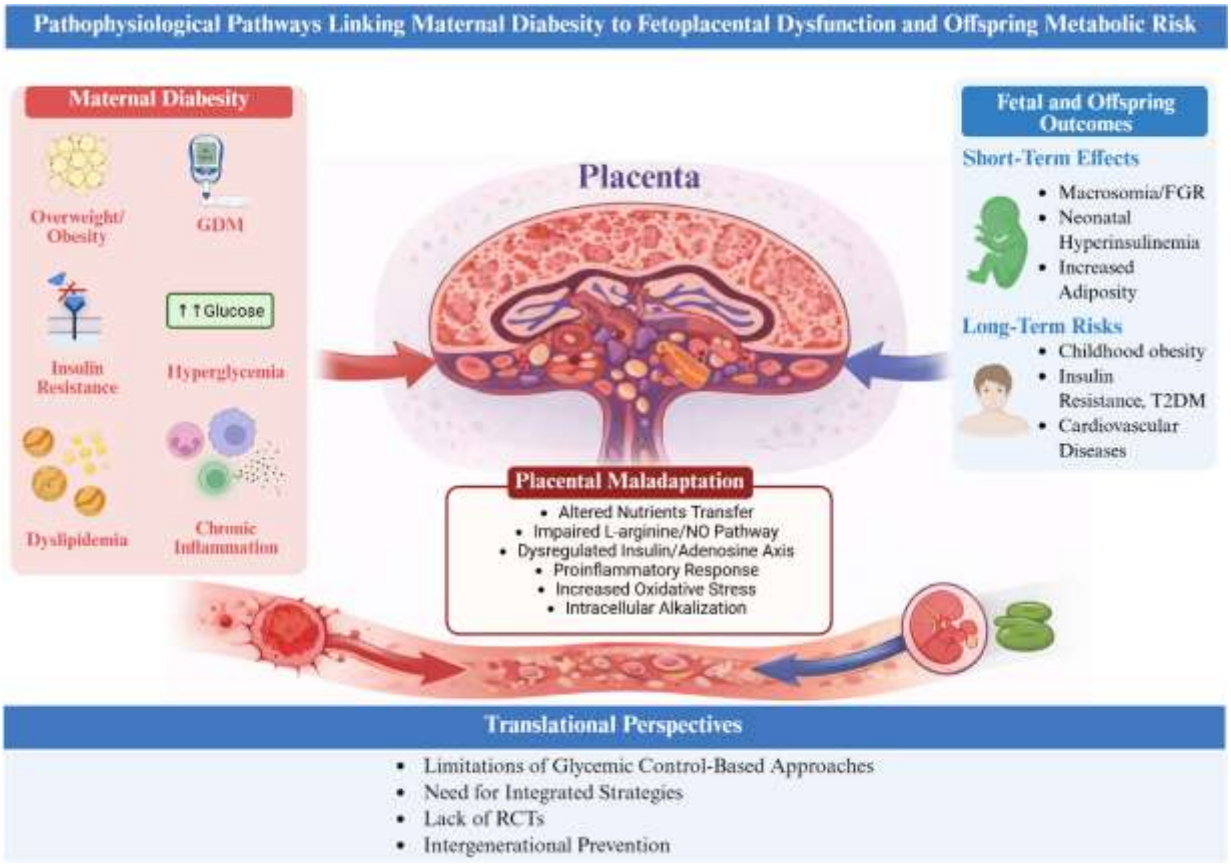

Figure 1. Pathophysiological pathways linking maternal diabesity to fetoplacental dysfunction and offspring metabolic risk. Created with BioRender.com, accessed on 16 December 2025. GDM, gestational diabetes mellitus; FGR, fetal growth restriction; T2DM, type 2 diabetes mellitus; NO, nitric oxide; RCTs, randomized controlled trials

5. Limitations

This review has several limitations. First, it is narrative rather than systematic in nature. Although major databases were searched and key systematic reviews and meta-analyses were used to identify primary studies, it is possible that some relevant publications were not captured. Second, formal risk-of-bias assessment tools were not applied uniformly across all included studies; instead, methodological quality was evaluated qualitatively. Consequently, the relative weighting of individual studies in the synthesis is based on study design, sample size, and apparent methodological rigor rather than on standardized scoring systems.

6. Conclusions

Maternal diabesity induces early and persistent fetoplacental dysfunction through interconnected mechanisms including endothelial insulin resistance, oxidative and inflammatory stress, mitochondrial impairment, and activation of endoplasmic reticulum stress pathways, resulting in impaired placental vascular function and nutrient sensing. These alterations disrupt maternal–fetal exchange and contribute to fetal programming of adverse outcomes, including abnormal fetal growth (macrosomia or growth restriction), neonatal hyperinsulinemia, increased adiposity, and long-term susceptibility to childhood obesity, insulin resistance, type 2 diabetes, and cardiovascular disease.

From a translational perspective, these findings highlight the limitations of glycemic control-based management and the need for integrated strategies targeting metabolic, vascular, and inflammatory disturbances in diabesity. Early preconception and pregnancy interventions aimed at preserving placental vascular and mitochondrial function may be key to reducing adverse outcomes and interrupting intergenerational metabolic risk.

Disclosures

Author Contributions

Conceptualization, J.S. and M.S.-G.; methodology, M.S.-G.; formal analysis, M.S.-G.; investigation, J.S. and M.S.-G.; resources, J.S. and M.S.-G.; writing—original draft preparation, J.S. and M.S.-G.; writing—review and editing, J.S. and M.S.-G.; visualization, M.S.-G.; supervision, J.S.; project administration, J.S.; funding acquisition, J.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

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