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Gestational Diabetes Mellitus: Mechanisms Underlying Maternal and Fetal Complications

Jooyeop Lee[1,*], Na Keum Lee[2,*], Joon Ho Moon[2]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, Armed Forces Yangju Hospital, Yangju;
[2]Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea

Gestational diabetes mellitus (GDM) affects over 10% of all pregnancies, both in Korea and worldwide. GDM not only increases the risk of adverse pregnancy outcomes such as preeclampsia, preterm birth, macrosomia, neonatal hypoglycemia, and shoulder dystocia, but it also significantly increases the risk of developing postpartum type 2 diabetes mellitus and cardiovascular disease in the mother. Additionally, GDM is linked to a higher risk of childhood obesity and diabetes in offspring, as well as neurodevelopmental disorders, including autistic spectrum disorder. This review offers a comprehensive summary of clinical epidemiological studies concerning maternal and fetal complications and explores mechanistic investigations that reveal the underlying pathophysiology.

Keywords: Diabetes, gestational; Diabetes complications; Pregnancy complications, cardiovascular; Fetal development; Neurodevelopmental disorders

The Songwon Medical Scientist Award is the highest scientific award of the Korean Endocrine Society to honor an individual below 45 years old who has made excellent scientific contributions and planned outstanding research proposal to progress in the field of endocrinology and metabolism. The Songwon Medical Scientist Award is named after the pen name of Professor Kab Bum Huh, who had been emphasizing the importance of research and educations in field of not only endocrinology but also overall medicine. Professor Joon Ho Moon received the Songwon Medical Scientist Award at the 2024 Symposium for Academia, Research, and Industry & Autumn Congress of the Korean Endocrine Society in October 2024.

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that is first identified during pregnancy [1]. GDM is a common pregnancy complication, with its prevalence exceeding 10% of pregnancies globally, including in Korea, and is rising in parallel with the worldwide increase in obesity [2-5]. GDM not only increases the risk of adverse pregnancy outcomes such as preeclampsia (PE), preterm birth, macrosomia, neonatal hypoglycemia, and shoulder dystocia, but also induces maternal mental distress and increases the risk of postpartum type 2 diabetes mellitus and cardiovascular disease (CVD) in the mother

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Corresponding author: Joon Ho Moon
Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, 82 Gumi-ro 173beon-gil, Bundang-gu, Seongnam 13620, Korea
Tel: +82-31-787-8133, **Fax:** +82-31-787-4070, **E-mail:** moonjoonho@snu.ac.kr

*These authors contributed equally to this work.

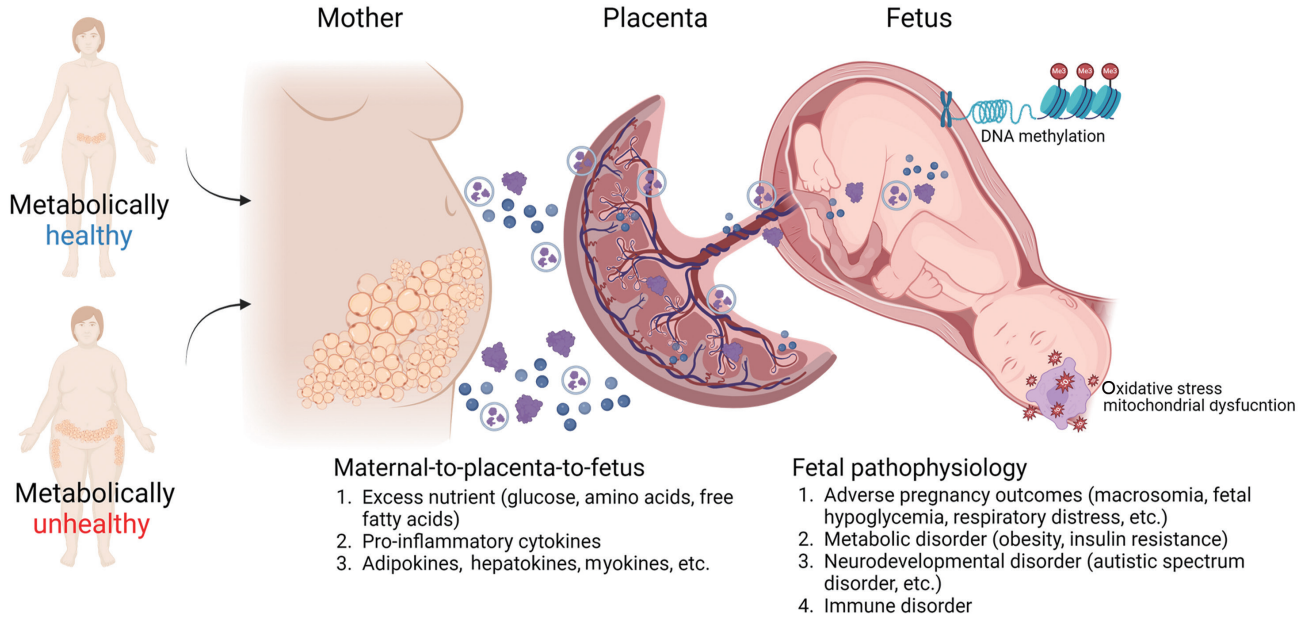

Fig. 1. Maternal metabolic health and fetal pathophysiology: impact of adipokines and cytokines on fetal development. Maternal metabolic health plays a critical role in regulating the secretion of adipokines, such as adiponectin and leptin, as well as pro-inflammatory cytokines, including interleukin 1β and tumor necrosis factor α. These molecules can cross the placenta, impacting fetal physiology, chromatin structure, and immune priming, thereby potentially contributing to adverse fetal outcomes.

[6-8]. A prospective cohort study demonstrated that women with a history of GDM experienced a rapid decline in β-cell secretory capacity and insulin sensitivity compared to those without a history of GDM after delivery [9]. Therefore, identifying factors that modulate maternal insulin secretory function and insulin sensitivity is crucial to help prevent postpartum diabetes and its vascular complications. Children born to mothers with GDM face an increased risk of obesity, diabetes, and neurodevelopmental disorders, including autistic spectrum disorder [10-12]. However, the underlying mechanisms remain poorly understood. With advances in omics technology, analyses of metabolic organs, including maternal adipose tissue, liver tissue, placental tissue, and fetal umbilical cord blood (CB), have been attempted to clarify the underlying pathophysiological mechanisms for maternal and fetal complications of GDM (Fig. 1). This review presents a comprehensive summary of clinical epidemiological studies on maternal and fetal complications, as well as mechanistic investigations that elucidate the underlying pathophysiological mechanisms.

MATERNAL COMPLICATIONS OF GDM

Postpartum type 2 diabetes mellitus

Women with GDM face an increased risk of developing type 2 diabetes mellitus or prediabetes after childbirth. While some may return to normal glucose tolerance (NGT) postpartum, a significant number continue to progress toward diabetes as they age. A 20-year follow-up study in the United States found that 40% to 60% of women with GDM went on to develop postpartum diabetes. Another United States study observed that among women with gestational diabetes, 30% developed diabetes within the first year after delivery, with an additional 5% diagnosed each subsequent year [13,14]. In Korea, a prospective cohort study reported a cumulative incidence of postpartum diabetes of 24% over a median follow-up of 4 years, with an expected incidence of 50% during an 8-year follow-up period among women with a history of GDM [15]. The risk of developing postpartum diabetes in women with GDM is 7 to 10 times higher than in women without a history of GDM [6,7,13].

Risk factors for progression to type 2 diabetes mellitus include maternal age, family history of diabetes, glycemic indices during pregnancy, and genetic predisposition, all of which are non-modifiable after delivery [7,13]. In a study of 634 Korean women with a history of GDM, 21 genetic variants associated with type 2 diabetes mellitus were genotyped. Variants located near cyclin-dependent kinase inhibitor 2A/2B (*CDKN2A/2B*) and hematopoietically expressed homeobox (*HHEX*) were linked to early conversion (≤8 weeks postpartum) to postpar-

tum diabetes, while variants near CDK5 regulatory subunit-associated protein 1-like 1 (*CDKAL1*) were associated with late conversion (>1 year postpartum) [15]. Genetic information may thus serve as a valuable tool for predicting the risk of type 2 diabetes mellitus. Choi et al. [16] investigated the association between a genome-wide polygenic risk score (PRS) and the risk of developing incident type 2 diabetes mellitus in cohorts of women with a history of GDM from diverse ancestries. A 1-standard deviation increase in the PRS was associated with a 1.44-fold increased risk of developing incident type 2 diabetes mellitus, and a PRS in the top 10% was linked to a 2.86-fold increased risk.

Taking into account non-modifiable risk factors, clinicians should prioritize improving modifiable factors, which include lactation, regular physical activity, a healthy diet, postpartum weight loss, and improved body composition [7,17-20]. The association between the modulation of these modifiable risk factors and improvements in insulin secretion or insulin sensitivity is further discussed below.

Cardiovascular disease

Women with GDM exhibit a higher risk of diabetes-related complications, particularly an increased risk of CVD [21-25]. The American Heart Association recently issued a scientific statement indicating that women with GDM face a two-fold increased risk of developing CVD [26,27]. Typically, women who develop GDM present with higher body mass index (BMI) and poorer metabolic profiles prior to pregnancy, characterized by elevated total cholesterol, triglycerides, and insulin resistance, alongside reduced levels of high-density lipoprotein cholesterol [28,29]. Over time, women with a history of GDM consistently demonstrate poorer cardiometabolic risk profiles, resulting in a higher incidence of obesity and metabolic syndrome compared to women without GDM [30,31]. More strikingly, women who maintained normoglycemia following a delivery complicated by GDM were unable to eliminate their future cardiovascular risk, as indicated by a greater than two-fold prevalence of positive coronary artery calcium scores (26.3% vs. 12.9%) [32], suggesting that GDM serves as a critical risk factor for metabolic diseases as well as CVD.

Several studies have demonstrated that lifestyle intervention programs can improve the cardiometabolic risk profiles of women with a history of GDM [33,34]. However, evidence is limited regarding the effectiveness of these lifestyle changes in preventing CVD in this demographic. Low participation rates in trials are often linked to factors such as lack of motivation and inadequate awareness of the associated risks, which pose significant obstacles to the successful implementation of lifestyle modifications [35]. The American Heart Association and the American College of Cardiology guidelines recommend dietary interventions that emphasize the consumption of vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts. They also recommend reducing the intake of sweets, sugar-sweetened beverages, and red meats. These dietary guidelines should be enforced through proper nutritional counseling to reduce cardiovascular risk in non-pregnant individuals [36]. Strategies such as smoking cessation, hypertension prevention and management, regular exercise, and maintaining a healthy weight should also be adopted to prevent CVD. It is plausible to suggest that the lifestyle modification measures for women with a history of GDM may not significantly differ from those recommended for women without a history of GDM.

Postpartum weight loss in Korean women with a history of GDM significantly improved blood pressure, lipid profile, body fat percentage, insulin sensitivity (Matsuda index), and β-cell function (disposition index) [18]. Other studies have shown that a longer duration of lactation is associated with a reduced risk of maternal hypertension [37], steatotic liver disease [38,39], and CVD-related hospitalization and mortality [40]. To prevent postpartum CVD, clinicians should consider a woman's obstetric history when evaluating her CVD risk, as a history of PE, preterm birth, and placental abruption are independent risk factors [26]. Additionally, increasing antenatal awareness of the potential long-term risks of CVD, along with reliable follow-up and postpartum screening, is essential for improving compliance and long-term health outcomes [41].

MATERNAL INSULIN SECRETION

During pregnancy, insulin resistance increases physiologically due to changes in various hormones. To compensate for this resistance, pancreatic β-cells enhance their insulin secretion and expand in mass. However, this compensation is expected to induce cellular stress [42-45]. An animal study assessing the effects of repeated delivery found that multiparous β-cells lost their proliferative capacity, which is essential for compensating for insulin resistance. These cells also displayed features of aging and senescence [46]. Additionally, multiparous β-cells exhibited shortened telomere lengths and higher expression levels of p16 (Cdkn2a), indicating β-cell aging and functional impairment associated with pregnancy and delivery.

Impairments in β-cell function affect women with GDM not only during pregnancy but also postpartum, increasing their risk of developing type 2 diabetes mellitus. Women who later progressed to type 2 diabetes mellitus exhibited reduced β-cell function, as evidenced by lower insulinogenic index and disposition index [15,47,48]. A sustained decrease in insulin secretion during the oral glucose tolerance test (OGTT) in the postpartum period has been linked to the development of a prediabetic state in women with a history of GDM [49]. A study from China has shown that a significant reduction in homeostasis model assessment of β-cell function correlates with a higher likelihood of developing postpartum type 2 diabetes mellitus [50]. Given the crucial role of insulin secretion in the progression of postpartum diabetes, clinicians should focus on identifying factors that affect insulin secretion in these individuals and advocate for interventions that can modify these factors.

Among the genetic risk factors for the progression to type 2 diabetes mellitus, variants including *CDKN2A/2B*, *HHEX*, and *CDKAL1* have been associated with impaired β-cell function [15,51]. The adenylate cyclase 5 (*ADCY5*) gene is also linked to impaired insulin secretion in women with a history of GDM, thereby increasing the risk of developing postpartum diabetes [52].

Fortunately, some steps can be taken to improve β-cell function in women with a history of GDM. In a Korean study, lactation was shown to improve β-cell function, with effects lasting up to 4 years after delivery [20]. Specifically, lactating women experienced a 40% increase in the disposition index. Weight loss not only enhanced insulin sensitivity (Matsuda index) but also β-cell function, as indicated by improvements in both the insulinogenic index and disposition index [18]. Additionally, postpartum weight reduction in multiparous women was linked to enhanced insulin secretory function [46]. Xiang et al. [53] found a strong association between weight gain and a decline in β-cell secretory capacity, as measured by the disposition index. Therefore, weight reduction can significantly improve β-cell insulin secretion.

Pancreatic β-cells from a mechanistic perspective

A recent genome-wide association study on GDM analyzed data from 12,332 cases and 131,109 controls from the FinnGen cohort, identifying 13 loci associated with GDM, nine of which were newly discovered [54]. Notably, the melatonin receptor 1b gene (*MTNR1B*) has been recognized as having a significant impact on GDM, while also sharing some genetic predispositions with type 2 diabetes mellitus. Overexpression of MTNR1B in insulin-secreting β-cells significantly enhances the inhibitory effect of melatonin on insulin release, primarily by reducing cyclic adenosine monophosphate levels, a critical signaling molecule for insulin secretion [55].

Kenna et al. [56] utilized differentially methylated circulating free DNA as a minimally invasive biomarker to assess β-cell death in women with GDM. The results showed that these women had elevated fasting glucose levels and reduced amounts of β-cell-derived insulin DNA, suggesting compromised insulin production and hyperglycemia.

Maternal β-cell expansion during pregnancy is crucial for maintaining glucose homeostasis. Multiple endocrine neoplasia type 1 (*MEN1*) and its protein product, menin, are believed to be key regulators in this process. Mice with β-cell-specific overexpression of *Men1* exhibited a phenotype similar to human GDM, characterized by glucose intolerance and reduced β-cell mass [57]. The expression of menin is influenced by prolactin and progesterone, indicating that abnormalities in lactogenic or steroid hormone signaling pathways could contribute to GDM and postpartum diabetes. Lactogenic hormones enhance signal transducer and activator of transcription 5 (STAT5) phosphorylation and its nuclear accumulation, which increases STAT5 binding and upregulates B-cell lymphoma 6 (Bcl6) expression in the β-cells of pregnant mice. During pregnancy, the transcriptional factor forkhead box M1 (FoxM1), which is involved in cell cycle regulation, is upregulated in maternal islets. In contrast, FoxM1 knockout in the pancreas results in no increase in β-cell proliferation, elevated menin and nuclear p27 levels, and the development of GDM [58]. Furthermore, placental lactogen stimulates FoxM1 expression in cultured islets, with FoxM1 playing a vital role in lactogen-driven β-cell proliferation *in vivo.*

During lactation, plasma prolactin levels increase, stimulating the production of serotonin (5-hydroxytryptamine [5-HT]) in β-cells, which improves both insulin secretory function and cell proliferation [59-62]. Additionally, 5-HT derivatives may act as direct antioxidants, supporting β-cell survival under oxidative stress [20].

MATERNAL INSULIN SENSITIVITY

Pregnancy triggers significant changes in insulin sensitivity due to hormonal fluctuations [63]. Women who exhibit reduced insulin sensitivity during pregnancy are at an elevated risk of developing postpartum diabetes [64]. Changes in insulin sensitivity before and during delivery, can substantially affect the likelihood of postpartum diabetes in women with GDM. Son et al.

[65] investigated the risk of postpartum type 2 diabetes mellitus by measuring changes in insulin sensitivity, using the Matsuda index at the time of GDM diagnosis and again at 2 months postpartum (ΔMatsuda index). They found that the incidence of prediabetes or type 2 diabetes mellitus 4 years postpartum decreased across the ΔMatsuda index tertiles (51.3%, 48.1%, and 36.4%). Higher muscle mass after delivery was associated with lower risk of type 2 diabetes mellitus suggesting the close association between insulin sensitivity and postpartum metabolic health [66].

To date, no well-designed trials have explored the direct relationship between CVD and the Matsuda index in women with a history of GDM. In one study, the Matsuda index, measured at 8 years postpartum, was identified as an independent predictor of both diabetes and metabolic syndrome at 15 years postpartum [67]. Several follow-up studies have shown that women with a prior history of GDM are at an increased future risk of developing metabolic syndrome [68,69], which is strongly linked to CVD [70]. Therefore, insulin resistance in women with GDM may contribute to an increased long-term risk of CVD.

Prasad et al. [52] identified genetic variants of ADAM metallopeptidase with thrombospondin type 1 motif 9 (*ADAMTS9*) that are associated with an increased risk of postpartum diabetes, particularly in relation to insulin resistance. They also explored the possibility that the increased risk of postpartum diabetes in women with a history of GDM could be linked to the insulin receptor substrate 1 (*IRS1*) genetic variant, which is associated with increased insulin resistance.

Molecular biomarkers associated with insulin resistance in women with GDM have been identified. Research indicates that elevated levels of branched-chain amino acids (BCAAs) can predict the risk of developing type 2 diabetes mellitus after pregnancies affected by GDM [71-73]. The metabolism of BCAAs may contribute to insulin resistance through the accumulation of toxic metabolites, which can impair β-cell mitochondrial function and promote insulin resistance [74]. Additionally, BCAAs may activate the mammalian target of rapamycin (mTOR) pathway, leading to the phosphorylation of insulin receptor substrate 1 and subsequent disruption of insulin signaling [75]. High postpartum levels of insulin-like growth factor 1 (IGF1) and low levels of insulin-like growth factor binding protein-2 (IGFBP2) are significant risk factors for the development of type 2 diabetes mellitus [76]. A study of Danish adults from the general population found that both low and high normal levels of IGF1 are associated with insulin resistance [77].

MicroRNAs (miRNAs) also contribute to the exacerbation of insulin resistance. By inhibiting the target gene peroxisome proliferator-activated receptor-α, miR-518d can disrupt the homeostatic balance between cellular fatty acid and glucose metabolism. This disruption may increase insulin resistance and contribute to the development of GDM [78].

Among the various risk factors associated with postpartum type 2 diabetes mellitus, modifiable factors such as postpartum body weight, lactation, physical activity, and diet influence maternal insulin sensitivity [20,79]. A prospective cohort study, which included 418 Korean women with GDM and an average baseline BMI of 23.3 kg/m^2 [18], found that those in the highest tertile of postpartum BMI change (who gained weight, with a BMI increase of 1.6 kg/m^2) had approximately twice the risk of developing diabetes compared to those in the lowest tertile (who lost weight, with a BMI decrease of –1.8 kg/m^2). Individuals who lost weight after delivery showed improvements in insulin sensitivity, while those who gained weight experienced a significant decline in insulin sensitivity and were unable to compensate by increasing their insulin secretion during the follow-up period.

Lactation is well known to enhance insulin sensitivity. This protective effect against postpartum diabetes can last for up to 30 years after childbirth [80,81]. Additionally, lactation increases energy expenditure by as much as 500 kcal per day, a rise attributed to the demands of breast milk production. In Korean women diagnosed with GDM, the Matsuda index was significantly higher in those who were lactating at 2 months postpartum and in those who had lactated previously, up to 4 years following delivery [20]. Furthermore, prior lactation is linked to improved insulin sensitivity not only in women with GDM but also in women of reproductive age within the general population [82-84].

Adipose tissue from a mechanistic perspective

Adipose tissue is a key metabolic organ that regulates metabolic processes through the secretion of adipose-derived factors, including adipokines and exosomal proteins. During pregnancy, women undergo gestational weight gain (GWG), which may lead to adipose tissue dysfunction and insulin resistance. Excessive maternal weight gain can result in maternal obesity, which not only leads to the development of type 2 diabetes mellitus and other complications but also adversely affects fetal outcomes [85].

Several studies have demonstrated that reduced levels of circulating adiponectin are linked to fetal overgrowth in GDM [86,87]. Aye et al. [88] reported that in pregnant women with

obesity, increased ubiquitination of adiponectin is associated with lower levels of total circulating adiponectin. This reduction impacts maternal insulin resistance and influences fetal growth. Another study explored the potential role of omental visceral adipose tissue (VAT) dysfunction in the metabolic complications associated with GDM. It compared patients diagnosed with GDM to those exhibiting NGT. The findings revealed notable adipocyte hypoplasia and a reduction in total IRS2 in the VAT of obese patients with GDM. Additionally, these patients displayed elevated circulating levels of leptin and adipsin, suggesting a correlation between VAT dysfunction and metabolic complications in GDM [89].

Musumeci et al. [90] characterized the immune cell and cytokine profiles in patients with GDM and NGT, revealing elevated levels of the pro-inflammatory cytokines interleukin (IL)-6 and IL-17A in obese patients with GDM. They also found that natural killer (NK) cell and T-cell phenotypes were modified in these patients, displaying an increased monocyte cluster compared to those with NGT. Research has recently begun to explore transcriptomic and proteomic analyses using adipose tissue.

Chen et al. [91] investigated alternative polyadenylation in adipose tissue from patients with GDM and controls. They found a significant elongation of the 3' untranslated region in the leucine rich repeat containing 25 (*LRRC25*) gene in the adipose tissue of GDM patients. This elongation was associated with reduced translation levels of genes related to metabolism and inflammation in omental adipose tissue.

Adipose tissue-derived exosomes, which facilitate interorgan communication, have recently been identified as regulators of placental functions. In pregnant patients with GDM, the release of exosomes from adipose tissue was found to be significantly higher (1.7-fold) compared to those with NGT. Additionally, differences were observed in mitochondrial dysfunction, the sirtuin signaling pathway, oxidative phosphorylation, and dopamine receptor signaling between GDM and NGT.

In placental cells, glycolysis- and gluconeogenesis-related genes were found to be upregulated by GDM-derived exosomes [92]. Li et al. [93] suggested a GDM mouse model, and adipose-derived stem cells (ADSCs) were collected to investigate their role in inducing insulin resistance via small extracellular vesicles (sEVs). Proteomic analysis revealed high levels of thrombospondin 1 (Thbs1) in sEVs from ADSCs/GDM, and targeting Thbs1 with the peptide LSKL restored insulin sensitivity in both alpha mouse liver 12 (AML12) cells and GDM mice by inhibiting Thbs1 expression in sEVs.

Liver from a mechanistic perspective

GDM serves as an early indicator of insulin resistance, which plays a crucial role in the onset of non-alcoholic fatty liver disease (NAFLD). In the Coronary Artery Risk Development in Young Adults (CARDIA) cohort, which included 1,115 participants, 124 women reported a history of GDM. Those with GDM demonstrated a significantly higher crude risk of NAFLD at 14%, compared to 5.8% in those without GDM [94]. In another study, mothers with GDM had a 50% greater risk of developing NAFLD, while offspring born to GDM-complicated pregnancies had approximately a two-fold elevated risk of developing NAFLD compared to those from non-GDM pregnancies [95].

Nevertheless, there is still a lack of mechanistic studies on liver in insulin resistance in GDM. Zhu et al. [96] examined the longitudinal relationships between levels of gamma-glutamyl transferase (GGT) and alanine aminotransferase (ALT), and markers of insulin secretion and resistance from early to mid-pregnancy. Their findings suggest that elevated GGT levels during early and mid-pregnancy, along with a progressive increase over this period, may play a role in the development of GDM. Recent studies have also examined the association between liver biomarkers and lipids in GDM. In a cohort of 9,148 pregnant women, those in the highest quartile of liver function index—which includes ALT, aspartate aminotransferase, GGT, alkaline phosphatase, and the hepatic steatosis index—showed a significantly increased risk of developing GDM. Furthermore, a causal relationship between ALT levels and GDM was established through Mendelian randomization analysis [97].

FETAL COMPLICATIONS OF GDM

Fetal hyperinsulinemia and overgrowth

Hyperglycemia occurring in the middle to late stages of pregnancy increases the levels of amino acids and fatty acids in maternal blood. This leads to an excessive transfer of nutrients to the fetus through the placenta [98]. A surplus of nutrients causes the fetal pancreatic β-cells to secrete insulin. As a result of maternal hyperglycemia, fetal hyperinsulinemia occurs, which promotes the excessive growth of insulin-sensitive tissues such as the liver, adipose tissue, and heart. Fetal abdominal overgrowth can be detected using ultrasound as early as 24 to 28 weeks of gestation [99,100]. This ultimately increases the risk of delivering a large for gestational age (LGA) infant in women with GDM.

Several factors have been reported to be associated with an increased risk of LGA, including maternal obesity [101]. A higher pre-pregnancy BMI has been linked to an increased risk

of LGA infants among Korean women with GDM [102]. Although it might be inferred that Korean mothers could have a lower risk of macrosomia compared to Caucasian mothers due to generally lower BMI levels, one interethnic study found that the incidence of macrosomia was similar between East Asians and Caucasians, with both groups showing rates ranging from 3% to 4% [103].

The risk of LGA infants may increase depending on the metabolic phenotype of the mother. Studies involving Canadian and European women with GDM have shown that those predominantly characterized by insulin resistance are more strongly associated with LGA than those with either lower insulin secretion alone or a combination of both factors [104,105]. In contrast, a study involving Chinese women found that insufficient insulin secretion, or a combination of impaired insulin sensitivity and secretion, is linked to a higher risk of LGA [106,107]. A study in Korea demonstrated that women in the insulin-resistant group faced a greater risk of LGA compared to those in the insulin-sensitive group [102]. Further research is warranted to investigate the relationship between GDM subtypes and adverse outcomes across various racial and regional populations.

Childhood obesity and type 2 diabetes mellitus

Metabolic disturbances have been observed in the offspring of mothers diagnosed with GDM, extending beyond the perinatal period into childhood and early adulthood. Notably, the prevalence of childhood obesity is higher among children born to mothers with GDM. A retrospective cohort study in the United States, which included 82 children exposed to maternal GDM and 379 unexposed children aged 6 to 13 years, demonstrated that exposure to maternal GDM was significantly associated with higher BMI, larger waist circumference, increased subcutaneous abdominal fat, and a higher subscapular-to-triceps skinfold thickness ratio [108]. Additionally, a subgroup analysis from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study in Hong Kong indicated a significant, albeit modest, increase in BMI at age 7 years, with mean values of 15.3 kg/m^2 for offspring of mothers with GDM compared to 15.0 kg/m^2 for those of normoglycemic mothers [109]. In contrast, a study assessing body composition in Korean children (mean age 5 years) of women with GDM found no significant difference in BMI compared to the control group; however, body fat mass was higher and lean body mass was lower [10]. Furthermore, body fat mass in children has been reported to positively correlate with maternal blood glucose levels during pregnancy [10]. Children of East Asian mothers with GDM show a less significant increase in BMI than their counterparts from other ethnic backgrounds. Therefore, to accurately evaluate adiposity and future cardiometabolic risk in Asian offspring of mothers with GDM, it is advisable to perform body composition analyses and/or skinfold thickness measurements.

Metabolic disturbances have also been observed in later adolescence. Recent findings from the HAPO follow-up study indicate that children, aged 10 to 14 years, born to women with mild GDM have a 21% increased risk of overweight and obesity. This risk in offspring has been shown to be associated with maternal blood glucose levels during pregnancy [110].

A higher prevalence of impaired glucose tolerance and diabetes has been observed in the offspring of mothers with GDM, including those whose mothers had pre-existing diabetes. In a longitudinal study spanning over 10 years, the incidence of impaired glucose tolerance in children born to mothers with GDM was significantly higher (19.3%) than that in the control group (2.5%) [111]. This development of impaired glucose tolerance in these children was associated with the maternal blood glucose levels during pregnancy. Additionally, the level of insulin in the amniotic fluid has been identified as a predictive marker for impaired glucose tolerance in offspring [111]. Moreover, maternal glucose levels during pregnancy showed a linear relationship with the glucose levels of offspring, as measured by the 75 g OGTT and glycosylated hemoglobin levels, independent of both maternal and child BMI [112,113].

Neurodevelopment disorders

Several studies have shown that offspring exposed to maternal GDM, infection, and hyperglycemia during pregnancy have an increased risk of developing autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) [12,114]. Research indicates that immune dysregulation, inflammation, and mitochondrial dysfunction play significant roles in the neural tissues of individuals with ASD [115,116]. In a study that exposed the mouse fetal brain to maternal inflammation, single-cell RNA sequencing (scRNA-seq) was conducted to analyze transcriptional gene expression [117]. This analysis revealed that maternal immune activation specifically triggers the integrated stress response in male offspring, but not in female offspring, through a mechanism dependent on IL-17A. Further research demonstrated that mouse offspring displaying autism-like traits from prenatal maternal inflammation exhibited an increased susceptibility to intestinal inflammation later in life. This susceptibility was driven by IL-17A, which induced immune-primed phenotypes through alterations in the maternal

gut microbiota that subsequently modified the chromatin structure of naive CD4+ T-cells postnatally [118].

MECHANISMS UNDERLYING FETAL COMPLICATIONS OF GDM: DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Placental dysfunction

The placenta is crucial for fetal development, maternal health, and the overall success of pregnancy. It facilitates the transfer of vital nutrients such as glucose, amino acids, and fatty acids from the mother to the fetus via diverse transport systems, thereby regulating fetal growth [119]. Placental dysfunction significantly contributes to pregnancy complications, including PE, GDM, and intrauterine growth restriction, all of which can have enduring impacts on the health of both mother and child.

The placenta is a complex organ derived from trophoblast cells and extraembryonic mesoderm [120]. Trophoblast cells differentiate into villous and extravillous types. Villous cytotrophoblasts (VCTs) fuse to form the syncytiotrophoblast (SCT), which constitutes the outer layer of chorionic villi and facilitate maternal-fetal exchange. Extravillous trophoblasts (EVTs) remodel uterine arteries to increase placental blood flow, independent of maternal vasomotor control [121,122]. Some studies have reported that trophoblast cells regulate the fetus-maternal interface, playing a critical role in placental development and function. Wnt and epidermal growth factor activation, along with transforming growth factor-β, histone deacetylase, and Rho-associated protein kinase inhibition, enables long-term culture of human trophoblast stem cells for studying placental development [123]. The TEA domain transcription factor 4 (TEAD4) regulates the self-renewal of trophoblast progenitors, and its loss causes embryonic lethality and recurrent pregnancy loss, highlighting the role of the Hippo signaling pathway in early pregnancy loss [124]. In another study, placental secretome and peptidome analysis showed elevated soluble fms-like tyrosine kinase 1 (sFLT1)/macrophage migration inhibitory factor (MIF) and angiopoietin 2 (ANGPT2)/MIF ratios in GDM, suggesting that these may serve as potential biomarkers for pregnancy complications [120]. The somatomammotroph family of hormones secreted by the placenta, including prolactin, growth hormone (GH), and placental lactogens, regulates maternal metabolism and insulin production, supporting fetal growth [125,126]. Recently, many groups have been investigating placental transcriptomic profiles using scRNA-seq, identifying various cell subtypes along with their specific marker genes. Suryawanshi et al. [127] created a detailed transcriptomic map of the first-trimester human placenta and maternal decidua through scRNA-seq of 14,341 and 6,754 cells, respectively, revealing critical gene signatures, transcription factors, and cell type interactions essential for early pregnancy development. In integrative single-cell and cell-free plasma RNA transcriptomics, gene expressions vary among distinct trophoblast cell types, underscoring their unique roles in placental function. VCTs expressed single domain globin Cgb (*CGB*), growth hormone 2 (*GH2*), and insulin like 4 (*INSL4*) for hormone synthesis. The SCT is marked by major histocompatibility complex class I-G (*HLA-G*), cytochrome P450 family 19 subfamily A member 1 (*CYP19A1*), and pappalysin 2 (*PAPPA2*), which play roles in immune tolerance. EVTs expressed matrix metallopeptidase 11 (*MMP11*), spondin 2 (*SPON2*), and gastrokine 1 (*GKN1*), which are associated with migration and invasion [128]. Liu et al. [129] characterized trophoblast cell types, reflecting their unique roles in placental development. Cytotrophoblasts expressed syncytin-2 for fusion into the SCT, as well as hormones like *INSL4* and glycoprotein hormones, alpha polypeptide (*CGA*), while EVTs serve as endocrine cells. Additionally, macrophage subclusters were identified, represented by apolipoprotein E (APOE), complement C1q C chain (C1QC), and colony stimulating factor 1 receptor (CSF1R), underscoring their role in clearing cellular debris during placental development.

Yang et al. [130] found 235 differentially expressed genes (DEGs) between GDM and control groups, including the amino acid transporter genes solute carrier family 1 member 2 (*SLC1A2*) and *SLC1A6*. *SLC1A2* was specific to the SCT, while *SLC1A6* was predominantly expressed in EVTs. Recently, a single-cell atlas constructed from control, PE, and GDM individuals revealed alterations of trophoblast cells and macrophages [131]. In particular, the decidual macrophage subcluster was upregulated in both PE and GDM, with gradual increases in the expression of alkaline phosphatase (ALPL), cytidine deaminase (CDA), peptidyl arginine deiminase 4 (PADI4), and zinc finger DHHC-type palmitoyltransferase 18 (*ZDHHC18*) observed along the differentiation trajectory. Recent scRNA-seq studies of placental tissue have primarily shown the distribution of trophoblast cells, limiting their ability to elucidate pathogenic mechanisms between maternal and fetal interactions. Furthermore, GDM and obesity share metabolic changes such as increased insulin resistance and inflammation, making it difficult to distinguish GDM-specific effects at the cellular level. Considering these points, an in-depth analysis of placenta-fetal immune profiling using various approaches, including scRNA-seq and assay for transposase-

accessible chromatin with sequencing (ATAC-seq), is essential to understand maternal-fetal interactions.

Insights from umbilical cord blood analysis

Fetuses exposed to maternal hyperglycemia exhibit an increased susceptibility to developing glucose intolerance, macrosomia, and associated preterm birth [132-134]. Umbilical CB, rich in proteins primarily released by the placenta, contains peptides and metabolites that play significant roles in fetal development. Characterizing these components could lead to the discovery of reliable biomarkers and enhance our understanding of fetopathy complications [135]. One study determined the methylation status of 68 cytosine-phosphate-guanine (CpGs) in umbilical cord tissue DNA from healthy newborns. Higher methylation of the retinoid X receptor alpha (*RXRA*) gene was independently associated with reduced childhood fat mass, while endothelial nitric oxide synthase showed mixed results across cohorts [136]. El Hajj et al. [137] reported on the impact of GDM on the epigenome of offspring by analyzing CB from 251 newborns (88 from dietetically treated GDM mothers, 98 from insulin-dependent GDM mothers, and 65 from non-GDM mothers). The results revealed significantly lower methylation levels of the maternally imprinted mesoderm specific transcript (*MEST*) gene in both GDM groups than in controls, which may increase the risk of obesity later in life. Other groups demonstrated the relationship between insulin receptor expression and DNA methylation in the context of GDM. Results showed that CB glucose levels were positively linked to methylation at CpG-AP-2 and SP1, while homeostasis model assessment of insulin resistance and insulin levels were not significantly associated with CB methylation [138]. Adiponectin (adiponectin, C1Q and collagen domain containing [AdipoQ]) is a critical hormone produced by adipose tissue that regulates insulin sensitivity, lipid homeostasis, and energy metabolism. In CB cells, DNA methylation analysis of the AdipoQ gene locus revealed that GDM-exposed newborns exhibited significant hypomethylation at R2 CpG1, which correlated inversely with relative birth weight [139]. Serotonin (5-HT) is also important for neurodevelopment and physiological processes related to metabolism. The relationship between maternal metabolic factors and CB methylation of serotonin-related genes (5-HT transporter, *SLC6A4*, monoamine oxidase A [MAOA], and 5-HT receptor type 2A [HTR2A]) indicated that *SLC6A4* methylation inversely correlated with prepregnancy BMI and GWG, while *HTR2A* methylation was positively correlated with GWG [140]. Xie et al. [141] performed proteomics by liquid chromatography-mass spectrometry/mass spectrometry. They found potential markers, such as soluble transferrin receptor, ceruloplasmin, apolipoprotein E, and inositol 1,4,5-trisphosphate receptor 1, which show promise as clinical markers for early screening of PE in GDM patients.

Metabolic risk in offspring

The offspring of mothers with diabetes are at increased risk of developing type 2 diabetes mellitus, possibly due to pancreatic islet dysfunction. Casasnovas et al. [142] used an infusion rat model in which a vascular catheter was placed in pregnant Sprague-Dawley rats to induce localized hyperglycemia by directly infusing glucose into the left uterine artery. RNA sequencing of fetal rat islets revealed a transcriptome associated with diabetes and inflammation. The findings indicated that hyperglycemia during late gestation led to the downregulated expression of genes such as regenerating islet-derived protein 3-gamma (*Reg3g*), regenerating islet-derived protein 3-beta (*Reg3b*), gamma-aminobutyric acid type A receptor subunit pi (*Gabrp*), and *Mmp7* in both weanling and adult offspring.

Furthermore, the hippocampal transcriptome of F1 male offspring exhibited increased expression of genes such as S100 calcium binding protein B (S100b), histamine receptor H3 (Hrh3), dopamine receptor D2 (Drd2), G protein-coupled receptor 88 (Gpr88), meis homeobox 2 (Meis2), and neurotrophin-3 (Ntf3), suggesting that intrauterine hyperglycemia may impair recognition memory [143]. Analysis of differentially methylated genes in F1 sperm and hippocampal gene expression in F2 offspring revealed 56 hypermethylated genes in F1-GDM sperm, which were associated with downregulated expression in the F2-GDM hippocampus, including genes such as A kinase anchoring protein 7 (*Akap7*), calcium/calmodulin dependent protein kinase 2 beta (*Camk2b*), DLG associated protein 1 (*Dlgap1*), and Wnt family member 5A (*Wnt5a*). These genes play roles in synapse structure, neuron development, and glial differentiation, with CpG hypermethylation predominantly found in coding sequences and intron regions. Govindarajah et al. [144] proposed a mechanism for the persistence of hematopoietic memory in adult offspring exposed to GDM. It is essential to recognize that the nucleotide binding and oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) and advanced glycation end product receptor (AGER) pathways are implicated in the establishment of gestational diabetes hematopoietic memory in offspring, which is associated with sterile placental inflammation. ATAC-seq of lineage-c-Kit+Sca-1+ (LSK) cells from GDM offspring indicated increased DNA methyltransferase 1 (DNMT1) methylation related to oxidative

stress and inflammation, suggesting that DNMT1 upregulation and subsequent changes in its methylome are critical in maintaining hematopoietic memory. Therefore, studies that analyze epigenetic alterations are vital for elucidating pathogenic mechanisms in maternal-fetal interactions.

CONCLUSIONS

This review provides a comprehensive overview of the increased risks of complications for both mothers and infants following delivery in GDM. It also explores the underlying mechanisms responsible for these complications and discusses the relevant research that elucidates their pathophysiology. Prospective cohort studies have shown that weight loss, lactation, physical activity, and a healthy diet can help prevent postpartum type 2 diabetes mellitus and may also improve CVD risk factors in mothers. However, evidence from interventional trials that supports a reduction in disease risk remains limited. Furthermore, in real-world settings, significant challenges exist in motivating mothers to engage in intensive lifestyle modifications and in facilitating their participation in clinical trials.

Exposure to *in utero* hyperglycemia in offspring has been linked to an increased risk of obesity, type 2 diabetes mellitus, and neurodevelopmental disorders. However, research into whether these risks stem from genetic predispositions or epigenetic modifications is still limited. To develop effective strategies for preventing or mitigating these complications, it is crucial to conduct further basic and translational research to identify the critical factors underlying these adverse outcomes. Investigations into maternal-fetal metabolic pathophysiology are expected to provide deeper insights into the etiology of maternal-fetal complications, thereby contributing to advancements in maternal and child health.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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ORCID

Jooyeop Lee *https://orcid.org/0000-0001-8632-5014*
Na Keum Lee *https://orcid.org/0009-0004-1398-3365*
Joon Ho Moon *https://orcid.org/0000-0003-1897-0905*

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