

Mechanisms linking hyperglycemia in pregnancy to cardiovascular system dysfunction in offspring

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ABSTRACT

Hyperglycemia in pregnancy (HIP) is a high-glycemic state that occurs during pregnancy, and gestational diabetes mellitus (GDM) is the major cause of it. Studies reveal that GDM has long-term adverse impacts on mothers and offspring, such as maternal type 2 diabetes, premature birth and stillbirth in newborns, cardiovascular disease, and metabolic disorders in adult offspring. In recent years, studies on the transcription level of GDM and metabolomics have provided new insights into the pathophysiological mechanism of GDM. This article reviews the transcriptional levels and metabolomics studies involving GDM and cardiovascular dysfunction in the offspring, which may provide insight to the long-term health of pregnant women and offspring.

Keywords: Pregnancy · GDM · Transcriptomics · Metabolomics · Glucose · Insulin resistance

Introduction

Diabetes may be characterized as a metabolic disturbance associated with structural and functional impairment to many tissues and organs, especially the heart, blood vessels, eyes, nerves, and kidneys. The pathophysiology and etiology of hyperglycemia in pregnancy appear correlated with hormonal dyshomeostasis and may be significantly impacted by the simultaneous influence of genetic and environmental factors. Indeed, there is a gradual increase in insulin response to nutritional stimulation during pregnancy, consistent with progressive insulin resistance (1).

Gestational hyperglycemia occurs when pancreatic beta cells can no longer adequately respond to increased insulin demand during pregnancy. Gestational diabetes mellitus (GDM) is diabetes first diagnosed during pregnancy and may occur anytime during the pregnancy (most likely after 24 weeks) (2). Pregnant women who have pre-existing

diabetes - type 1 diabetes, type 2 diabetes, or monogenic diabetes - may likely experience in utero hyperglycemia (3). Therefore, hyperglycemia in pregnancy (HIP) includes GDM and diabetes in pregnancy according to the International Federation of Gynecology and Obstetrics, but GDM remains the predominant cause of HIP (75–90%) (4,5).

With increasing gestational weight gain and maternal age, the incidence of GDM has increased over recent decades (6–8). The Hyperglycemia and Adverse Pregnancy Outcome Study suggests that the frequencies of GDM varied between 9.3% and 25.5% (mean 17.8%) (9), depending on the population characteristics and diagnostic criteria. With the increasing incidence of HIP, more evidence suggests that HIP has a variety of long- and short-term effects on both mothers and offspring (**Figure 1**), including preeclampsia, prelabour rupture of membranes, hyperbilirubinemia, polyhydramnios, hypocalcemia and hypomagnesemia, stillbirth, macrosomia, preterm delivery, and hypoglycemia in the newborn, and greater risk of developing respiratory distress (10–14). Long-term adverse health implications reported in the offspring of HIP mothers include overweight and subsequent obesity, cardiovascular diseases, increased incidence of neuropsychiatric and neurodevelopmental problems, and ophthalmic diseases.

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In addition, GDM is strongly linked to metabolic disorders in adult offspring, including insulin resistance, low acute insulin secretory responses, type 2 diabetes, persistently impaired glucose tolerance, and adipokine changes (15–17). Interestingly, it has been observed that these metabolic consequences are more frequent in female offspring, suggesting sex-dependent adverse effects (15,18,19). In addition, the female offspring of GDM mothers are more likely to experience GDM during pregnancy, which is regarded as a vicious circle (20). Although the prevalence of HIP is increasing, hyperglycemia-induced impairment to the offspring's cardiovascular system is unknown. Therefore, the aim of this review is to highlight and summarize the currently known molecular and metabolic mechanisms that contribute to offspring cardiovascular system dysfunction, which may provide new insights and therapeutic options for improving the long-term health of GDM women and offspring (**Figure 2**).

1. Gene expression and transcriptional production

Pancreatic β -cells help the body respond to the decline in the mother's insulin sensitivity. When blood glucose level decreases during normal physiology, the activity of glucokinase, the main glucose sensor in pancreatic β -cells, is adaptively increased, thereby enhancing insulin secretion (21,22). Meanwhile, prolactin and placental lactogen play a maladaptive part in the occurrence and development of GDM. It has been demonstrated that pregnant mice lacking prolactin receptors develop GDM (23). The lack of placental lactogen leads to β -cell proliferation, reduction of Menin (24), induction and regulation of FoxM1 (25), and activation of the paracrine/autocrine loop that increases serotonin production (26,27).

Small non-coding RNAs (ncRNAs) constitute about 60% of human genome transcripts. They can bind to the special regions of mRNAs and regulate signal pathways, embryonic development, and pathological processes of diseases through translation inhibition or messenger degradation (28–33). Based on their length and morphology, ncRNAs that are currently of interest in research include microRNAs (under 200 ribonucleotides), long non-coding RNAs (lncRNA, longer than 200 ribonucleotides), and circular RNAs (with the covalent binding between the 3' and 5' ends) (34, 35). Studies have shown that ncRNA-mediated intracellular and intercellular communication can be observed under both physiological and pathological conditions (34, 36, 37). The expression of ncRNAs is essential for the formation of pancreatic islet cells (38). Despite their physiological significance, several ncRNAs have been found to be correlated with insulin resistance and β -cell dysfunction. In particular, the abnormal regulation of ncRNAs in utero may influence the expression of target genes in offspring and cause long-term adverse events, such as obesities and cardiac diseases (39).

Additionally, Li et al. have suggested that the low expression of plasma small nucleolar RNA host gene 17 (SNHG17) may be used as a predictor in the first semester of GDM pregnancy (40). lncRNA maternally expressed

gene 3 (MEG3) is abnormally upregulated in the blood, placental chorionic trophoblast cells, and umbilical vein endothelial cells of pregnant women with GDM, and it impairs the endothelial function of the fetus through the action of miR-345-3p and microRNA-370-3p targets and the AKT signaling pathway (41, 42). A follow-up of 400 women showed that plasma MEG8 levels in GDM patients are significantly elevated. In particular, researchers are able to distinguish future GDM patients from healthy pregnant women through the plasma MEG8 levels one month before GDM diagnosis (43). Moreover, Zhang et al. showed that the expression level of lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) in the case group is significantly higher than that of healthy pregnant women, suggesting that MALAT1 may also be a novel biomarker (44, 45).

Not only that, in obese mice with leptin deficiency, miR-375 was absent and thus unable to maintain insulin homeostasis, and thus develop severe diabetes (46). ncRNAs also play an important role during pregnancy - studies have found that the placenta-associated microRNA is a modulator of peroxisome proliferator-activated receptor (PPAR). PPAR is a receptor involved in capacity control, lipid metabolism and inflammation, and has been shown to be associated with type 2 diabetes (47). A recent study compared the expression of miR-143 in pharmacologically treated GDM patients and normal pregnant woman in placental tissues in vivo, and found that as a protective target, miR-143 participates in the abnormal function of mitochondria in the placenta of GDM patients by regulating enzymes in glycolysis (HK-2) (48). Additionally, a 2016 study found that at 37–40 weeks of gestation, the expression of miR-98 in the placental tissue of GDM mothers was significantly increased. The same investigators used the human cell line JEG-3 to demonstrate that miR-98 regulates the glucose uptake factor Trpc3 by directly regulating Mecn2 (49). Studies have also shown that during pregnancy, the expression of miR-218 and miR-338-3p are down-regulated, while the expression of miR-144 and miR-451 is up-regulated. Specifically, under the action of estradiol and incretins, miR-338-3p regulates the proliferation of pancreatic β -cells (50). Some investigators believe that the microRNA from placenta exosomes may reflect the metabolic state of the placenta. Therefore, Nair et al. compared the microRNA differences between the chorionic villi explants in the GDM group and the control group through next-generation sequencing. Gene target and ontology analyses show differentially expressed miRNAs participating in pathways that regulate cell migration and carbohydrate metabolism (51). Since the fetus is constantly exchanging bodily fluids with the mother in utero, ncRNAs may likely be exchanged and influence the gene expression of the offspring. Based on the regulatory effect of ncRNA on the occurrence and development of GDM, as well as its presence in peripheral blood, ncRNAs may be used as biomarkers of GDM in pregnancy, and may even be utilized to predict the future metabolism of the fetus (39).

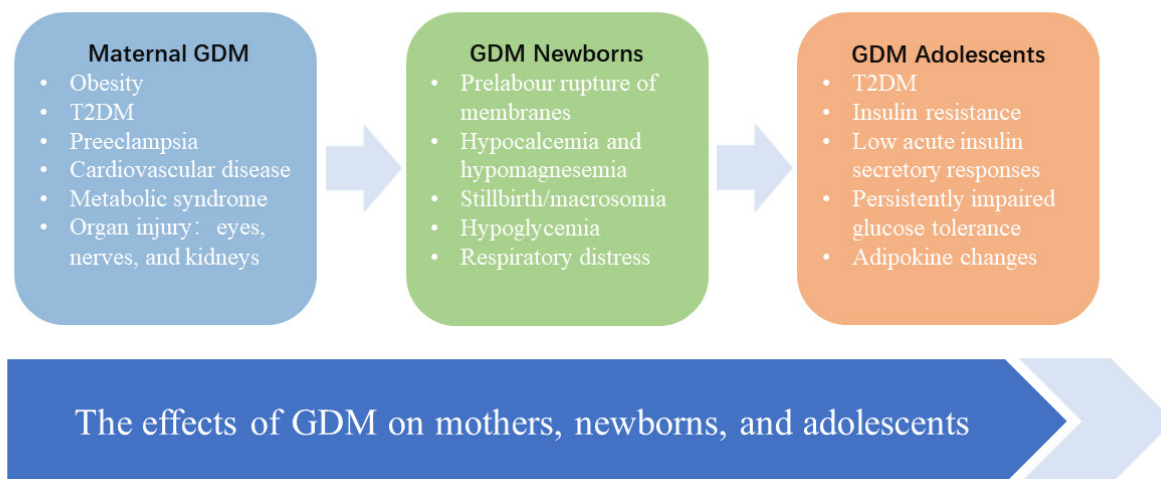


Figure 1. A variety of effects on both GDM mothers and offspring. In addition to maternal target organ damages, GDM can lead to obstetric accidents in newborns and metabolic dysfunction in adolescents. The adverse health effects of GDM in various groups are listed above.

2. Metabolomics

The high glucose environment in utero can lead to fetal metabolic disorders. This complex metabolic regulation process may partly explain the dysfunction of the cardiovascular system in the offspring. As a discipline of systematic and full-term research on low molecular weight compounds in tissues and body fluids, metabolomics can contribute to the elucidation of the mechanism of this process and reveal potential therapeutic targets and biomarkers (52). In recent years, the primary focus of metabolomics data is on the detection of pregnancy body fluid compounds of GDM mothers, including the detection of pregnant women's serum, plasma, and urine. A few other metabolomics studies collected and examined other non-traditional samples, such as fetal cord blood, urine, and meconium. Additionally, since childhood and adolescence are important periods for the development of obesity and diabetes (53, 54), there are also some metabolomics studies that examined samples from children and adolescents who have GDM mothers (55). However, despite the multitude of existing GDM metabolomics studies, a clear conclusion of metabolic profile characteristics still cannot be determined. To address this problem, future studies need to increase the number of samples in the group, compare the differences in metabolomics of samples before and after oral glucose tolerance test (OGTT), and improve the diversity of the subjects, such as their race, ethnicity, age, and living conditions.

2.1. Maternal Lipid Metabolism

A study involving 592 mothers and children tracked metabolomics data from 6-14 years old (late childhood) and 12-19 years old (adolescents) and found that female offspring that exhibited in utero hyperglycemia had increased levels of phosphatidylcholine, diacylglycerol, and phosphatidylethanolamine, which can increase the risk for obesity and higher metabolic dysfunction (56). Other

studies have also shown that acetone and 3-hydroxybutyric acid are elevated in GDM, suggesting increased fatty acid catabolism (57). Indeed, another pregnancy cohort study of 178 GDM and 180 normal pregnant women showed that in addition to metabolites that participate in fatty acid oxidation, other metabolites were changed; the investigators found 17 metabolic compounds were altered (58). In the third trimester, from the control group to the mild increase in blood glucose group to the GDM group, the total fatty acids (FAs) and several specific FAs in the serum of pregnant women showed a gradually increasing trend for metabolites (59). Other studies utilizing LC-MS and GC-MS have confirmed that several lysophospholipids, taurine bile acids, and long-chain polyunsaturated fatty acid derivatives in GDM pregnant mothers are different than normal pregnancy control mothers, which may partly be responsible for changes in redox balance and low degree of inflammation (60).

2.2. Maternal Amino Acid Metabolism

Amino acids are indispensable nutrients for intrauterine growth, and the fetus carries out protein synthesis and oxidation. In addition to providing the amino acids, the placenta is also involved in protein transamination and the synthesis of some non-essential amino acids (61). Some non-essential amino acids are metabolized and delivered through interorgan cycling between the fetal liver and the placenta. The liver metabolizes glutamine (Gln) and glycine (Gly) and delivers them to the placenta as glutamate (Glu) and serine (Ser), respectively (62, 63). Therefore, the amino acid metabolism in the uterus is intimately connected to the growth of the fetus. The results of studies on mothers with type 1 diabetes show that the concentration of many amino acids increases during the first and third trimesters of pregnancy (64), which may suggest that in a state of high glucose in the uterus, the increase in amino acid metabolism and the sugar load affect fetal insulin secretion, thereby inducing

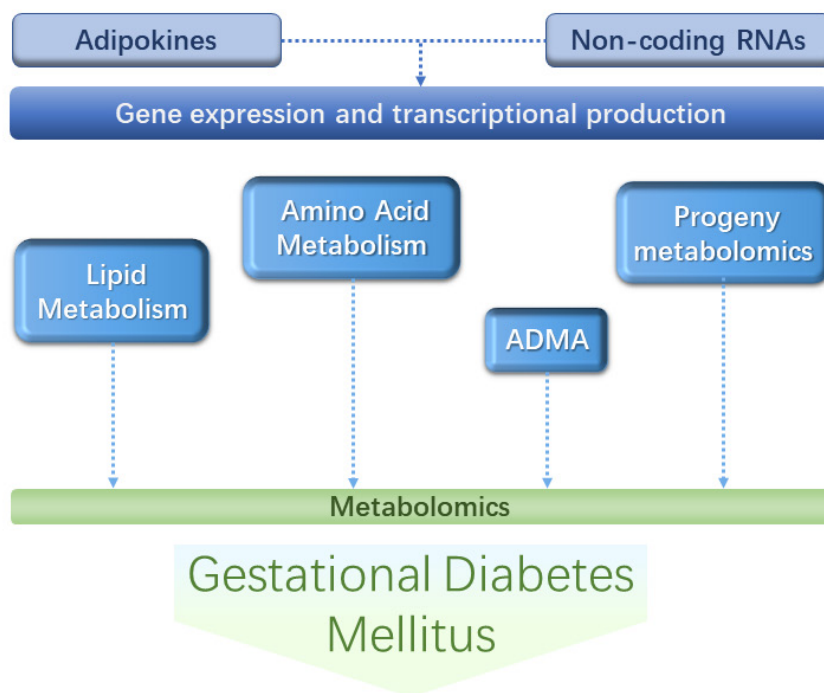


Figure 2. Conceptual diagram of associations among maternal GDM and offspring health outcomes throughout gestation to adulthood. The co-regulation of adipokines, lncRNA, and microRNA affect the metabolic changes and induce the occurrence of diseases and produce possible adverse consequences for offspring.

subsequent pathophysiological changes. Metabolomics studies of GDM mothers show that ketogenic amino acids and branched chain amino acids (BCAA) are released by skeletal muscle at a low rate and are mainly catabolized by the liver. Among them, the levels of fasting carnitine ester levels are lower, fasting β -hydroxybutyrate and free fatty acid levels are higher, and the levels of methionine, glycine, alanine, citrulline, and ornithine are significantly higher in GDM pregnant mothers relative to normal pregnant women. In normal pregnancy, proteolysis, ketogenic amino acids, and BCAA are catabolized in the liver. As a result, ketogenic amino acids are totally oxidized and gluconeogenesis is enhanced, thereby accelerating the urea cycle (65). The three common BCAA include leucine, isoleucine, and valine. In the past, researchers have found that BCAA is associated with obesity in childhood and adolescence and future insulin resistance, and studies have confirmed that nondiabetic people have lower BCAA levels compared with people who will develop type 2 diabetes later. Hence, BCAA may be a significant risk factor for diabetes (66–69). Indeed, an early study showed that the fasting and postprandial BCAA levels of the GDM population in the third trimester of pregnancy (30–39 weeks) are higher than those of the normal control pregnancy population (70). On the contrary, there are some studies showing that at 30–33 weeks and 37–41 weeks of pregnancy, there is no difference in the BCAA level in the plasma of GDM mothers relative to the normal control group. (61, 65). Some investigators believe that although BCAA may be used as a metabolic marker for predicting type 2 diabetes, it may not have the identical predictive power for GDM as

anthranilic acid, alanine, glutamic acid, serine, creatinine, and allantoin; these metabolites are remarkably different between GDM pregnant population and normal pregnant population (71).

It is worth noting that in the early pregnancy metabolic map, itaconic acid, cis-aconitic acid, and acylcarnitine can be used as serum biomarkers to distinguish GDM pregnant mothers from normal pregnant women, and can be used for predicting subsequent metabolic development of GDM mothers and offspring (72, 73). Studies have demonstrated that in the first trimester of pregnancy, there are remarkable differences in the levels of arginine, glycine, and 3-hydroxyisovalerate carnitine in serum samples of GDM pregnant patients compared with serum samples of normal pregnant women (74). Results from research on GDM have demonstrated increased hypoxanthine excretion due to hypoxia and enhanced gluconeogenesis for energy supply, as well as increased production of sugar-generating amino acids and cis-aconitic acid, suggesting the need for the increase in the tricarboxylic acid cycle (57). A study that collected nuclear magnetic resonance (NMR) spectra of GDM parturients' amniotic fluid (AF) during the second trimester of pregnancy for metabolomics testing showed that abnormal fetuses seem to suffer from changes in energy metabolism and renal dysplasia. The metabolic profile of the GDM population before diagnosis indicates that as the average level of glucose increases, several amino acids, creatinine, glycerophosphocholine, acetic acid, formic acid and other compounds show a slight downward trend (73).

2.3. Maternal Asymmetric Dimethylarginine (ADMA)

Endothelial dysfunction caused by reduced bioavailability of nitric oxide (NO) is considered an early cause of atherosclerosis. Asymmetric dimethylarginine (ADMA) is an endogenous NO synthesis inhibitor, which is closely related to amino acid metabolism and participates in the metabolic process of protein modification in the cytoplasm (75). Some studies believe that it is involved in the occurrence of endothelial dysfunction and subsequent adverse cardiovascular events (76). The results of some clinical studies have shown that ADMA levels are elevated in various metabolic diseases like insulin resistance, type 2 diabetes, chronic heart failure, atherosclerosis, hypercholesterolemia, hypertension, and chronic renal failure (55). Other studies have also suggested that ADMA can be used as an independent predictor of cardiovascular death and all-cause mortality (76–79). ADMA level has been shown to exhibit a gradually increasing trend among normal pregnant mothers, impaired glucose tolerance mothers and GDM mothers, which may be significantly positively correlated with the increase in insulin and gestational age (80–82). Moreover, some studies have found that severe endothelial dysfunction exists in both IGT and GDM patients in the third trimester and is directly related to blood glucose levels. Together, these studies provide evidence that ADMA may be involved in the pathophysiological mechanism of GDM (83).

2.4. Maternal adipokines that regulate metabolism

Some adipokines play an essential role in the pathophysiological mechanism of diabetes. Studies have shown that in the second trimester of pregnancy, overweight GDM women have higher levels of leptin than normal pregnant women (21–23). At the same time, the researchers also observed that adiponectin decreases in the first 1-3 months of GDM pregnancy (24, 25). Therefore, some researchers suggest that the ratio of adiponectin to leptin (usually < 0.33, at 6-14 weeks of pregnancy) may be a predictor of GDM (26). Additionally, in the third trimester of pregnancy, cytokines such as high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor alpha (TNF- α) in the serum of GDM women are higher than those of normal pregnant women (27–29). It has also been found that in the 24-28th week of pregnancy, the plasminogen activator inhibitor-1 (PAI-1) of GDM women is elevated significantly (29). Moreover, visfatin increases at 11-13 weeks of GDM women (30). In contrast, omentin-1 is reduced in the second trimester of GDM women (31). Studies have also reported that FABP4 is elevated in the first and third semesters (32–34), while plasma RBP4 levels are high in the first two months of GDM pregnancy (25, 35). Furthermore, in the third semester of GDM, some researchers have noted elevated levels of fibroblast growth factor-23 (FGF-23) (36).

2.5. Progeny metabolomics

In recent years, in addition to focusing on the metabolomics samples of GDM mothers, researchers have also examined the effect of GDM on the metabolomics of offspring. Studies have performed nuclear magnetic

resonance spectrum analysis on the umbilical cord serum of newborns and found that the offspring samples from GDM mothers have lower glucose levels than the control group, and detected the increase of pyruvate, histidine, alanine, valine, methionine, arginine, lysine, hypoxanthine, lipoprotein and lipid levels (84). Researchers have found that 14 meconium metabolism markers and 3 urinary metabolism markers, of which four meconium metabolism biomarkers (taurodeoxycholic acid, glycocholic acid, oxytrihydroxy leukotriene B₄, and DHAP (8:0) is closely involved in lipid metabolism (85). It is highly probable that the specific changes in GDM offspring after birth and even the susceptibility of diseases in adulthood may be due to alterations in lipid metabolism pathways (phospholipids, taurine-bound bile acids, and long-chain polyunsaturated fatty acid derivatives) (60).

Changes in the levels of endogenous biomarkers indicate that there is an increase in glucose, amino acids, and fatty acid assimilation in GDM, as well as the co-regulation of adipokines, lncRNA, and microRNA. The combined effect of these factors will affect fetal insulin secretion (86), which may induce the occurrence of diseases and produce possible adverse consequences for offspring by affecting lipid, amino acid, purine metabolism. Unbalanced lipid metabolism seems to be a characteristic feature of GDM.

Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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