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## Epigenetic modifications of placenta in women with gestational diabetes mellitus and their offspring

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### Abstract

Gestational diabetes mellitus (GDM) is a pregnancy-related complication characterized by abnormal glucose metabolism in pregnant women and has an important impact on fetal development. As a bridge between the mother and the fetus, the placenta has nutrient transport functions, endocrine functions, *etc.*, and can regulate placental nutrient transport and fetal growth and development according to maternal metabolic status. Only by means of placental transmission can changes in maternal hyperglycemia affect the fetus. There are many reports on the placental pathophysiological changes associated with GDM, the impacts of GDM on the growth and development of offspring, and the prevalence of GDM in offspring after birth. Placental epigenetic changes in GDM are involved in the programming of fetal development and are involved in the pathogenesis of later chronic diseases. This paper summarizes the effects of changes in placental nutrient transport function and hormone secretion levels due to maternal hyperglycemia and hyperinsulinemia on the development of offspring as well as the participation of changes in placental epigenetic modifications due to maternal hyperglycemia in intrauterine fetal programming to promote a comprehensive understanding of the impacts of placental epigenetic modifications on the development of offspring from patients with GDM.

**Key Words:** Gestational diabetes mellitus; Placental functions; Epigenetics; Offspring development

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**Core Tip:** Gestational diabetes mellitus is a pregnancy-related complication characterized by abnormal glucose metabolism in pregnant women and has an important impact on fetal development. The review aims to investigate the effect of abnormal placental function on offspring development in pregnant women with gestational diabetes from the perspective of epigenetics.

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## INTRODUCTION

Gestational diabetes mellitus (GDM) is a common metabolic disorder during pregnancy and refers to an abnormal glucose tolerance that occurs or is first observed during pregnancy. Epidemiological evidence shows that in recent years, the prevalence of GDM has been on the rise worldwide. The international prevalence rate of GDM varies from 6.6% to 45.3% [1], depending on the region, population and diagnostic criteria and the total prevalence rate of GDM in China is 14.8% [2]. Like type 2 diabetes, GDM is characterized by relative insulin deficiency caused by changes in the function and mass of  $\beta$  cells and an increase in insulin resistance [3]. The offspring of patients with GDM are more prone to suffer from congenital developmental abnormalities [4,5] and complications such as macrosomia, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, and later obesity, metabolic disorders and cardiovascular abnormalities [6,7]. GDM has become a public health issue of global concern.

The placenta plays a crucial regulatory role in maintaining fetal growth and development throughout pregnancy, as it has multiple functions, such as nutrient transport and endocrine functions. Moreover, abnormal placental functions can also induce a variety of fetal diseases and complications, such as fetal overnutrition or growth restriction. Previous studies have shown that metabolic abnormalities in GDM patients could damage the structure, morphology and functions of the placenta and lead to pathological changes, affecting the energy conversion between the mother and the fetus, and affecting fetal development [8]. In recent years, an increasing number of studies have shown that the placenta is associated with diseases such as obesity in offspring [9], cardiovascular diseases [10] and impaired neurodevelopment [11], implying the importance of the placenta during fetal development.

Studies have shown that pregnant women who are exposed to adverse conditions for a long time, such as smoking, alcohol abuse, lack of exercise, sleep deprivation, unhealthy dietary habits, and hormone use, may also experience changes in the epigenetic level of their placenta, leading to abnormal gene expression, which further results in alterations in placental function and metabolism [12] and an increase in the risk of GDM onset. GDM can also lead to epigenetic abnormalities in the placenta, such as changes in DNA methylation and miRNA expression, thereby affecting normal fetal development [13,14].

In this paper, with the placenta regarded as an important target organ through which GDM affects offspring development, the potential impacts of its functional and epigenetic changes on offspring development are reviewed, and the possible underlying mechanism is explored, providing a scientific basis for preventing abnormal development and ensuring the subsequent health of the offspring of patients with GDM.

## IMPACTS OF GDM ON PLACENTAL TRANSPORT FUNCTION

The placenta is a transient multifunctional organ responsible for the transport of nutrients from the mother to the fetus. GDM can affect the nutrient transport function of the placenta, increase or decrease the amount of energy delivered to the fetus, and thus affect fetal weight [15] (Table 1).

### *Impacts on placental glucose transport*

Glucose is the main energy source for the fetus and the placenta. The placental glucose transport function is affected by maternal glucose concentration, glucose transporters (GLUTs) and placental glucose metabolism [15] and is also regulated by insulin in early pregnancy [16]. For patients with GDM, the concentration of GLUT and glucose uptake in the basement membrane (BM) of the placenta increase, and the transport of maternal glucose to the fetus increases, leading to macrosomia [17,18]. However, a decrease in or deficiency of placental GLUT leads to abnormal conditions, such as fetal hypoglycemia and weight loss [19], indicating that placental GLUTs are crucial for fetal growth and development.

In the full-term placenta of GDM patients, the expression levels of GLUT-1, GLUT-4, and GLUT-9 increase and are positively correlated with fetal birth weight [17]. For GDM patients treated with insulin, placental glucose uptake and transport increase, and the expression level of GLUT-4 in the placenta is positively correlated with birth weight and subscapular fat thickness [17]. Similar findings were observed in animal models, *e.g.*, in the placenta of mice with GDM induced by a high-fat diet, the AMPK-GLUT-3 axis was impaired, and the expression of GLUT-3 in the placental plasma membrane decreased, resulting in reduced glucose uptake by the placental trophoblast and excessive glucose input into the offspring, which led to the overgrowth of the offspring [20]. These research results indicate that an intrauterine

**Table 1 Relationship between placental transport function and fetal weight in gestational diabetes mellitus**

Nutrient	Transporter	GDM model		Cell lines	Mechanism of action	Localization	Result	Ref.	
		Gestational age	Animal species						
Glucose	GLUT1	37+ wk gestation	-	-	-	P↑; BM↑	FBW (+); AFM (+), SSFM (+)	[17,18]	
		Full-term placenta	-	-	p-Akt and Erk↑	P↑	FBW↑	[23]	
	GLUT4	37+ wk gestation	-	-	-	P↑	SSFM (+); FBW (+)	[17]	
	GLUT9	37+ wk gestation	-	-	-	P↑	FBW (*)	[17]	
	GLUT3	-	db/+mice & HFD-induced C57B L/6j mice	-	AMPK↓	PM↓	FBW↑	[20]	
Amino acids	System A	-	-	Insulin stimulates PHT cell and PVE	p-Akt and Erk↑	PHT↑	FBW↑	[9]	
		-	-	TNF-α stimulation PHT cell	Erk; p38MAPK	PHT↑	FBW↑	[30]	
		-	-	IL-6 treat PCT	JAK/STAT	PCT↑	FBW↑	[31]	
		-	-	LPS and poly (I:C) treat PCT	TLR3 and TLR4↑	PCT↑	FBW↑	[32]	
	SNAT 1	37-41 <sup>+6</sup> wk gestation	-	-	-	IGF-I and mTOR↑	P↑	FBW (+)	[25]
		-	-	TNF-α stimulation PHT cell	Erk; p38MAPK	PHT↑	FBW↑	[30]	
		-	-	LPS and poly (I:C) treat PCT	TLR3 and TLR4↑	PCT↑	FBW↑	[32]	
	SNAT2	-	-	TNF-α stimulation PHT cell	Erk; p38MAPK	PHT↑	FBW↑	[30]	
		-	-	IL-6 treat PCT	JAK/STAT	PCT↑	FBW↑	[31]	
		-	-	LPS and poly (I:C) treat PCT	TLR3 and TLR4↑	PCT↑	FBW↑	[32]	
	SNAT3	-	-	IL-6 treat PCT	JAK/STAT	PCT↑	FBW↑	[31]	
	System L	-	-	MVM and BMs from GDM	-	MVM↑	FBW↑	[28]	
		-	STZ-induced SD rats	-	mTORC1↓	P↓	FBW↓	[46]	
Lipids	TG	-	-	Hight glucose and insulin treat PHT	-	PHT↑	FBW↑	[35]	
		-	HF/HCD induced C57BL/6j mice	-	CEH↑, TGH↓	P↑	FBW↑	[36]	
		37-42 wk gestation	-	Hight glucose treat PE	β-oxidation↓	P↑	FBW↑	[38]	
	EL	Full-term placenta	-	-	p-Akt and Erk↑	P↑	FBW↑	[41]	
	FAT	-	-	Hight glucose and insulin treat PHT	-	PHT↑	FBW↑	[35]	
		Full-term placenta	-	-	p-Akt and Erk↑	P↑	FBW↑, FBW (+)	[41,42]	

FABP4 A-FABP L-FABP	Full-term placenta	-	-	p-Akt and Erk↑	PHT↑, P↑	FBW↑	[34,40, 41]
FABP3, FABP4	-	-	High glucose and insulin treat PHT	-	PHT↑	FBW↑	[35]
FATP-1	Full-term placenta	-	-	p-Akt and Erk↑	P↑	FBW↑	[41]

P: Placenta; FBW: Fetal baby weight; SSFM: Subscapular fat mass; AFM: Abdominal; PM: Plasma membrane; BM: Basement membrane; PHT: Primary human trophoblast; PVE: Placental villous explants; PE: Placental explants; PTC: Primary trophoblast cells; CEH: Cholesterol ester hydrolase; MVMs: Microvillous plasma membranes; +: Positive correlation; \*: Correlation; FATPs: Fatty acids transport proteins.

hyperglycemic environment alters the expression of placental GLUTs and increases glucose transport between mothers and fetuses, thereby increasing offspring weight.

In addition, insulin can regulate glucose metabolism to promote fetal development in early pregnancy. Studies have shown that the phosphorylation of the insulin-like growth factor 1 receptor (IGF-1R) and increased expression of insulin receptor A (IR-A) in the placenta of GDM patients are associated with fetal overgrowth[21]. The ability of IGFBP to bind to the umbilical cord and placental stroma of patients with GDM is reduced, resulting in an increase in free IGF-1[22]; however, an increase in IGF-1 can activate insulin/IGF-1 signaling (Akt and Erk) in the placenta to increase placental GLUT-1 expression and fetal birth weight[23]. GLUT-4 in placental microvillous membranes (MVMs) increases placental glucose uptake under the regulation of insulin during early pregnancy, leading to an increase in glucose transfer to the fetus[16]. These results indicate that maternal hyperinsulinism regulates the activity and expression of placental GLUTs, which may accelerate fetal growth.

### Impacts on placental amino acid transport

Placental amino acid transport is mediated by proteins expressed in maternal-circulation-oriented MVM and fetal-circulation-directed BM. The placenta has 15 amino acid transport systems, such as system A, which is responsible for supplying small neutral amino acids (a Na<sup>+</sup>-dependent transport protein), and system L, which is responsible for supplying essential large neutral amino acids (a broad Na<sup>+</sup>-independent transporter protein)[24]. The activation of placental IRs by maternal hyperinsulinism leads to the activation of mammalian target of rapamycin (mTOR)[9,25], which is a key regulatory factor for placental amino acid transport[26] and can promote cell proliferation and fetal growth. There are significant differences between the concentrations of maternal amino acids and the concentrations of amino acids in cord blood from GDM patients, even with well-controlled blood glucose[27], indicating that GDM alters placental amino acid transport or metabolism.

In the case of fetal overgrowth, the ability of the placenta to transport amino acids is significantly improved in GDM patients[28]. The signaling activities of IGF-I and mTOR in the placentas of GDM patients with well-controlled blood glucose increased and were positively correlated with birth weight. In particular, the upregulation of the system A amino acid transport protein in the placenta increased the probability of macrosomic babies occurring in women with GDM[25]. Through experiments on primary human trophoblasts (PHTs) and placental villous explants, maternal hyperinsulinism was shown to activate placental IR signaling (Erk and Akt) pathways and improve amino acid transport in system A[9]. In the placenta of GDM patients, the mTOR signaling pathway is activated, pro-oxidant/pro-inflammatory factors increase[29], and the proinflammatory cytokines TNF- $\alpha$ [30] and IL-6[31] can upregulate the amino acid transport of system A in PHT by activating the Erk/p38 MAPK and JAK/STAT signaling pathways, respectively. The activation of the Toll-like receptor 3 (TLR3) or TLR4 signaling pathway could lead to insulin resistance in primary trophoblast cells and significantly increase the expression of system A amino acids (SNAT1 and SNAT2) and the uptake of related amino acids[32]. Other studies have shown that activation of the TLR4 signaling pathway is associated with increased uptake of system A amino acids stimulated by fatty acids (FAs) in PHT[33]. The L-system, another important placental amino acid transport system, is also involved in fetal weight programming. An increase in L-system-mediated leucine uptake in the placental MVM of a GDM patient with a baby large for gestational age (LGA) promoted placental leucine transport and facilitated the acceleration of fetal growth[28]. These results indicate that GDM increases the transport of amino acids in the placental system, leading to increased risks of fetal overgrowth and obesity.

### Impacts on placental lipid transport

The essential FAs required for fetal growth mainly rely on maternal supply and placental transport. Placental FA transport relies mainly on the activity of lipid hydrolases in the syncytiotrophoblast MVM and FA uptake by various FA transport proteins [FA transporters (FATs), FA binding proteins (FABPs), and FA transport proteins (FATPs), *etc.*] in the plasma membrane[34-36].

The high expression levels of the placental proteins PI3K p110 $\alpha$ , LXR $\alpha$ , FAS, and SCD1, which are related to lipid metabolism and lipoprotein lipase (LPL), in GDM may lead to the accumulation of placental triglycerides (TGs)[37]. Although the uptake and transport of placental FAs are not affected by maternal hyperglycemia, hyperglycemia reduces the  $\beta$ -oxidation of the placenta and thus leads to an increase in the placental TG[38]. Experiments on human placental explants have shown that the activity of carnitine palmitoyltransferase is inhibited by hyperglycemia, such that  $\beta$ -oxidation is reduced and esterification pathways are increased, leading to the accumulation of placental TG[39]. Another

animal experiment showed that maternal mice fed a high-fat/high-cholesterol diet (accompanied or not accompanied by GDM) had dysregulated placental lipid hydrolase activity, increased cholesteryl ester hydrolase activity, and decreased TG hydrolase activity; as such, excessive cholesterol was input into the offspring, resulting in an increase in liver lipids and the accumulation of placental TG, which may cause overgrowth[36]. These findings indicate that the oxidation of FAs is reduced and that the expression of placental proteins and TG hydrolases becomes imbalanced, which causes the deposition of placental TG; moreover, although maternal TG does not pass through the placenta, it can be decomposed by placental LPL, TG hydrolases and other lipases and subsequently infiltrate the placenta. A series of factors are associated with fetal overgrowth.

It has been reported that the expression of FABP4 is increased and that the expression of LPL is decreased in the male placenta of a GDM patient with macrosomia. Additionally, the mRNA expression level of angiopoietin-like protein 3 (ANGPTL3) is increased, and the activity of LPL is inhibited by ANGPTL3, which leads to an increase in the storage of liver adipocytes; moreover, FABP4 increases the FA gradient to promote the delivery of placental lipids to the fetus[40]. Other studies have shown an increase in the deposition of TG and the expression of FA transport proteins (FAT, FABP3, and FABP4) in the placenta of GDM patients[35]. Treatment of GDM with insulin could significantly increase the phosphorylation of Akt and Erk in the placenta and the expression of placental lipid carriers (FAT, A-FABP, and endothelial lipase) and promote the transfer of placental lipids to the fetus[41]. Several studies have shown that the expression of FAT and TLR4 in the placenta of GDM patients significantly increases and is positively associated with neonatal weight[42]. The ANGPTL3-4-8 axis regulates lipid transport and protein expression and is related to fetal birth weight, body length and placental weight[43]. However, the dysregulated expression of this axis in the placenta of GDM patients has an impact on placental lipid transport and protein expression. These results indicate that an increase in the placental lipid transfer gradient and in the transport of proteins due to an intrauterine high-glucose environment leads to the accumulation of fetal lipids, which may lead to an elevated fetal obesity level and increased neonatal body fat mass in GDM patients.

Although macrosomia is common in the fetuses of GDM patients, growth retardation is a common manifestation in GDM animal models. The pregnancy of STZ-induced GDM rats is characterized by placental enlargement and varying degrees of growth retardation in the offspring[44]. The placental IR pathway is altered by hyperinsulinism and activates the downstream endothelial carbon monoxide synthase to stimulate increased placental angiogenesis[45], thereby affecting placental nutrient metabolism. Animal and *in vitro* experiments have shown that amino acid transport proteins are downregulated in offspring with growth restriction, and the activity of placental mTORC1 is reduced in STZ-induced GDM rat models, resulting in a decrease in L-system amino acid transport proteins in the placenta, which is associated with intrauterine growth restriction and a reduced birth weight[46]. It has also been found in human and *in vitro* experiments that IL-15 is upregulated in the placenta of GDM patients and promotes trophoblast proliferation *in vitro* through the JAK/STAT signaling pathway, which is negatively correlated with neonatal weight[47].

## EFFECTS ON THE HORMONE SECRETION FUNCTION OF THE PLACENTA

Animal experiments have shown that the dysregulation of hormones secreted by the placenta during pregnancy may alter insulin signaling and adversely affect fetal growth[11,48]. A number of studies have shown that the level of human placental lactogen (HPL) in GDM patients increases during the third trimester of pregnancy, and the expression levels of HPL in mothers and umbilical cord blood are closely related to placental weight and birth weight[49,50]. Placental enlargement in GDM patients may cause an increase in the levels of growth hormone (GH) and HPL, induce maternal insulin resistance and stimulate the generation of fetal IGF-1 and insulin, thereby resulting in fetal fat deposition and overgrowth[51]. HPL can also regulate fetal growth and development *via* a certain mechanism. A targeted reduction in placental HPL in sheep can lead to early intrauterine growth restriction and a significant decrease in the birth weight of the offspring in the later stage[52]. GH[53] and HPL[54] significantly increased in the placenta of LGA pregnancies, whereas the expression levels of HPL[55] and GH[53] were reduced in small for gestational age pregnancies. These results indicate that placental HPL and GH jointly regulate fetal growth and development in utero.

In addition, insulin/IGF and adipokines secreted by the placenta are also important for fetal growth and development. The expression of the IGF-1-IGFBP-1 axis is dysregulated in the umbilical cord blood of GDM patients, and the opposite changes in IGF-1 and IGFBP-1 expression are observed. The increased bioavailability of IGF-1 caused by a reduction in IGFBP-1 leads to increased glucose uptake and utilization, increasing the risk of macrosomia[56]. Studies have shown a positive correlation between the risk of suffering from GDM and a higher level of IGF-1 in maternal blood[57,58]. Several studies have shown that the expression of IGFBP-1[59], IGFBP-2[58], IGFBP-3[60], and IGFBP-rP1[61] in the umbilical cord blood of GDM patients significantly decreases, leading to a reduction in the ability of IGFBP to bind to IGF-1 and IGF-2[60], whereby the level of free IGF-1 in umbilical cord blood[22] and the phosphorylation of IGF-1R in the placenta increase[21]. These changes improved the signaling activity of free IGF-1 and IGF-2 in umbilical cord blood. Moreover, several studies have shown that the fetal weight of GDM patients is significantly positively correlated with the expression of IGF-1[23,25,62] and IGF-2[63] in the placenta. Cellular experiments and clinical studies have also shown that GDM strengthens placental insulin/IGF-1 signaling, which activates downstream mammalian mTORC1 targets and increases placental nutrient transport[26], leading to fetal overgrowth, as its activation is positively correlated with birth weight[25, 64]. These results indicate that changes in the insulin/IGF signaling axis may be an important mechanism for fetal birth weight gain in GDM patients. In addition, GDM patients with macrosomia have higher levels of umbilical cord leptin (LEP) and resistin[65] and lower levels of the maternal adiponectin gene (*ADIPOQ*)[23]. However, the expression levels of LEP and resistin in the umbilical cord were positively correlated with the body weight of large-for-date fetuses, whereas

maternal ADIPOQ was inversely proportional to birth weight[65]. This may be because the phosphate site of IRS-1 was inhibited by low maternal ADIPOQ levels, which, together with insulin/IGF-1/mTOR signaling, regulated nutrients such as glucose, amino acids and lipids to stimulate fetal overgrowth[59,66]. These findings indicate that placental adipokines participate in insulin axis signaling to jointly regulate placental nutrient transport and fetal growth and development.

## IMPACTS ON PLACENTAL DNA METHYLATION

It has been reported that the epigenetics of the placenta play key regulatory roles in placental development and function [67]. The impacts of GDM on the global methylation of the placenta and the methylation of imprinted genes and metabolic genes may result in impairments to the placenta and intrauterine fetal development and even an increased susceptibility of the offspring to diseases such as obesity and metabolic syndrome in the later stage (Figure 1).

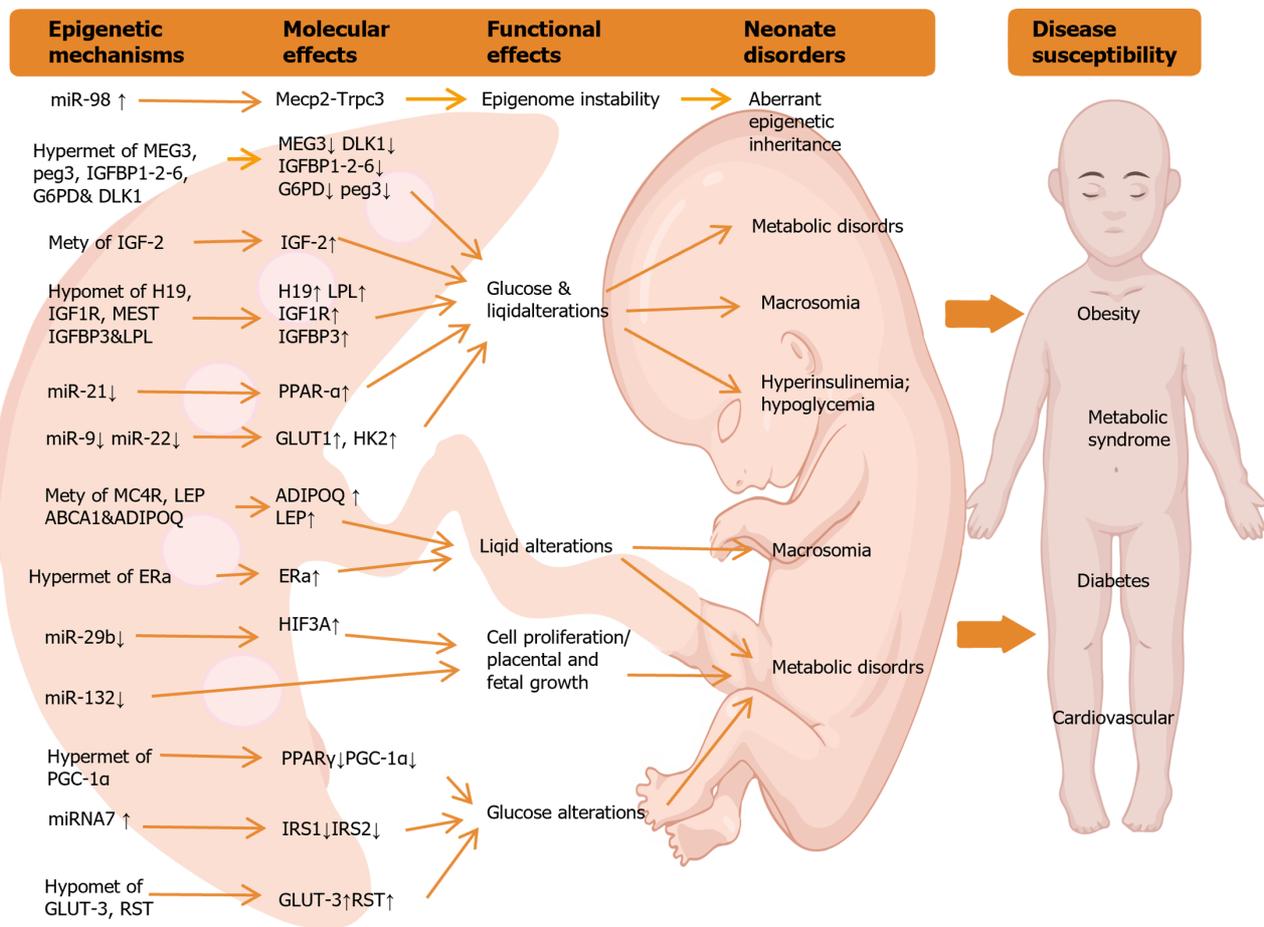
### **Global methylation of the placenta and methylation of imprinted genes**

A number of studies have shown that the methylation of a large number of genes in the placenta of GDM patients is associated with fetal weight. The differentially methylated position (DMP) of 11 genes in the placenta of GDM patients is associated with birth weight[68]. Among the differentially methylated genes in the placenta of GDM patients, 326 placental genes and 117 umbilical cord genes are also associated with neonatal weight[69].

Studies have shown that three CpG methylation sites in the DNA methylation region of the maternally expressed gene 3 (*MEG3*) on the maternal side of the placenta of GDM patients are significantly increased and are positively correlated with maternal blood glucose and fetal weight, whereas only one CpG position on the fetal side of the placenta is highly methylated and unrelated to fetal weight[70], indicating that maternal metabolic status alters the methylation level of the placenta and participates in fetal development. Some studies have shown that DNA methylation of the maternal imprinted gene mesoderm specific transcript (*MEST*) in the placenta of GDM patients significantly decreases and is related to GDM, possibly leading to the pathogenesis of GDM macrosomia. Researchers have also found that the methylation of *MEST* significantly decreases in the peripheral blood of adult obese individuals[71]. These results indicate that *MEST* is involved in the reprogramming of obesity in offspring and suggest the consequences of placental methylation on early exposure to an adverse intrauterine environment, including the tendency toward obesity in adult offspring. The hypermethylation of the imprinted gene *DLK1* on the fetal and maternal sides of the placenta in GDM patients led to a significant decrease in its gene expression and was positively correlated with fetal weight and maternal two-hour oral glucose tolerance test (OGTT) blood glucose concentration[72], indicating that the methylation of *DLK1* may be a potential mechanism for obesity and metabolic programming disorders in childhood and adulthood. Under the influence of a high-glucose environment, *IGF-2* and *H19*, which are also pairs of imprinted genes, exhibit variable methylation levels, and the expression level of *IGF-2* increases[73]; moreover, the expression of *IGF-2* is directly proportional to the occurrence of macrosomia[63]. Studies have shown that changes in the methylation and expression levels of placental imprinted genes in STZ-induced GDM mice led to the hypomethylation and increased expression level of *H19* and the hypermethylation and decreased expression level of *PEG3*; and the methylation changes of the imprinted genes could be reversed by transferring prokaryotic embryos of diabetic female mice into normal pregnant uteruses[74]. The hypomethylation of the paternally expressed genes *IGF1R* and *IGFBP-3* in the placenta and the high expression of these genes were negatively correlated with maternal blood glucose levels, and the increased expression of *IGF1R* mRNA was related to the birth weight of newborns, which may be involved in the pathogenesis of GDM macrosomia and increase the susceptibility of offspring to obesity[75]. These experiments indicate that alterations in the methylation of placental imprinted genes and their gene expression levels provide genetic information for fetal adipose tissue and metabolic programming and increase the susceptibility of offspring to metabolic diseases in the later stage.

### **Methylation of placental metabolic genes**

Placental methylation can also affect fetal development by regulating the expression of metabolic genes. Studies have shown that placental *LEP*, which is capable of regulating insulin signaling and participating in insulin resistance, is associated with the pathogenesis of GDM. The average methylation level of *LEP* at 23 CpG sites in the placenta of GDM patients was greater than that in the placenta of healthy pregnancies, and *LEP*, an adipokine for maintaining energy homeostasis, is capable of regulating fetal growth and placental nutrient exchange[76]. However, another study showed that the methylation level of *LEP* decreased in the placenta of GDM patients, and the DNA hypomethylation level of its gene locus (cg15758240) was negatively correlated with the expression level of *LEP* (a representative of neonatal obesity) in the fetus at birth and in early childhood obesity[77]. In addition, *ADIPOQ* and *LPL* are important metabolic genes in the placenta. The methylation level of *ADIPOQ* on the maternal side of the placenta is correlated with maternal two-hour OGTT blood glucose concentration, increased insulin resistance, and maternal *ADIPOQ* levels during pregnancy and after delivery, and higher adiponectin levels in umbilical cord blood are associated with fetal birth weight[78]. Adiponectin is the most abundant circulating hormone secreted by adipocytes and is regulated by the degree of insulin resistance. The methylation of adiponectin may lead to obesity, insulin resistance and glucose metabolic disturbance in offspring and increase the probability of suffering from type 2 diabetes in offspring. The methylation levels of the *LPL* proximal promoter and intronic CpG islands decreased in the placenta of GDM patients, wherein the hypomethylation levels of *LPL* at the CpG1 and CpG3 loci were negatively correlated with maternal blood glucose and high-density lipoprotein cholesterol (HDL-C), and the hypomethylation level of the *LPL*-CpG2 Locus was negatively correlated with the expression level of placental *LPL* mRNA and HDL-C in umbilical cord blood[79], indicating that the versatility of the methylation levels of *LPL* may be related to maternal and fetal metabolic profiles and involved in placental lipid transfer



**Figure 1 Role of placenta epigenetic modification in offspring development of gestational diabetes mellitus.** MEG3: Maternally expressed gene 3; IGF-1R: Insulin-like growth factor 1 receptor; LEP: Umbilical cord leptin; HIF3A: Hypoxia-inducible factor 3 subunit α; PGC-1α: Proliferator-activated receptor-γ coactivator-1α; GLUT: Glucose transporters.

and intrauterine programming of fetal adipose tissue. Another experiment also showed that a low DNA methylation level at the 3.4 CpG site in the placenta of GDM patients was positively correlated with birth weight and mid-childhood fat mass[80]. In addition, the methylation level of LPL in the placenta was inversely proportional to its gene expression, and LPL in placental syncytiotrophoblasts was capable of hydrolyzing TG-rich lipoproteins into FAs to increase maternal-fetal lipid transfer gradients and promote placental lipid transfer to increase fetal weight. These energy metabolism genes participate in the regulation of energy metabolism and insulin sensitivity, and adaptive changes may lead to sustained glucose metabolism disorders in both mothers and offspring.

Studies have shown that an increase in the nuclear receptor estrogen receptor α (ERα) protein and its mRNA level in extracellular trophoblasts on the maternal side of the placenta in GDM patients may be related to hypomethylation of the ERα promoter region[81]. Estrogen secreted by the placenta is an important regulator of fat metabolism and may participate in the programming of fetal fat metabolism in utero. The hypermethylation levels of IGFBP-1, IGFBP-2, IGFBP-6, and G6PD in the placenta of GDM patients were positively correlated with maternal fasting plasma glucose and one-hour blood glucose concentration after an OGTT. The methylation levels of IGFBP and G6PD were negatively correlated with their expression in the placenta. A decreased expression of IGFBP increases the availability of free IGF-1, contributing to the occurrence of macrosomia. Fetal birth weight was significantly negatively correlated with the expression of G6PD mRNA but was positively correlated with methylation[82]. The ATP-binding cassette transporter A1 (ABCA1) is a key regulator for placental lipid transfer. It has been reported that the hypermethylation level of ABCA1 on the maternal side of the placenta in pregnant women with impaired glucose tolerance is correlated with maternal HDL-C levels and two-hour OGTT blood glucose concentrations, and maternal blood glucose and HDL-C act together on the DNA methylation profile of ABCA1; moreover, the hypermethylation level of ABCA1 on the fetal side of the placenta is negatively correlated with TG levels in umbilical cord blood, and the hypomethylation level of ABCA1 in umbilical cord blood is negatively correlated with maternal two-hour OGTT blood glucose concentrations in the second trimester of pregnancy[83]. The difference in the methylation of ABCA1 between the placenta and the umbilical cord may be an adaptive response of the fetus to intrauterine hyperglycemia to compensate for the reduction in the placental transfer of maternal cholesterol, but it also leads to increased susceptibility to dyslipidemia, obesity, impaired endothelial function and cardiovascular diseases in the later stage. The melanocortin 4 receptor (MC4R) gene plays a crucial role in regulating metabolism by suppressing appetite and participating in energy control. The methylation levels of the CpG-1 and CpG-2 loci of the energy metabolism gene MC4R on the fetal side of the placenta in GDM patients decreased, whereas the

methylation level of the CpG-1 locus of MC4R on the maternal side of the placenta increased in pregnant women with a smoking habit and was related to maternal one-hour and two-hour OGTT glucose concentrations and low-density lipoprotein cholesterol (LDL-C) levels[84]. The spatial difference in the methylation levels of energy metabolism genes between the fetal side and the maternal side of the placenta may be a certain environmental adaptation change to protect the metabolic health of the offspring and reveal the complexity of DNA methylation.

Peroxisome proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ ), a transcriptional coactivator, is a regulator that adjusts nutritional energy homeostasis and metabolism between the placenta and the fetus during pregnancy and participates in the metabolic programming of the fetus. Studies have shown that maternal two-hour OGTT glucose concentrations in the second trimester of pregnancy are positively correlated with DNA hypermethylation at the PGC-1 $\alpha$  CpG locus in the placenta, and the degree of correlation increases with maternal weight and insulin resistance during pregnancy and is negatively correlated with the hypomethylation of PGC-1 $\alpha$  DNA in the umbilical cord[85]. The difference in methylation between the placenta and the umbilical cord may be an adaptive mechanism to the intrauterine high-glucose environment. In the placenta of GDM patients, the methylation of the PGC-1 $\alpha$  promoter increases, the expression of PGC-1 $\alpha$  mRNA decreases, and the downregulation of PGC-1 $\alpha$  in the placenta is negatively correlated with early fetal blood glucose[86]. The expression of PGC-1 $\alpha$  and peroxisome proliferator-activated receptor  $\gamma$  in the placenta of GDM patients decreased and was negatively correlated with that in the offspring during young adulthood[87]. The methylation of PGC-1 $\alpha$  may alter the methylation pattern of PGC-1 $\alpha$  in fetal endocrine organs (such as islets) and the sensitivity of other tissues to insulin, resulting in an increase in blood glucose and an increased risk of diabetes in offspring. The hypomethylation and increased expression of GLUT-3 and resistin in the placenta of GDM patients led to excessive placental glucose transport to the fetus and increased insulin resistance, thus giving rise to fetal glucose metabolism disorders and macrosomia[88].

In summary, changes in the methylation of placental metabolic genes may underlie the pathogenesis of obesity and other related metabolic diseases. These research data show that epigenetics provides valuable information for the programming of placental and fetal development and can guide future research directions, provide disease prediction information for clinical practice and facilitate the development of prevention and treatment measures.

### **Transgenerational effects of placental methylation**

In the STZ-induced GDM model, intrauterine hyperglycemia may induce hypermethylation of the imprinted gene *Dlk1-DMR* and hypomethylation of *IG-DMR* and *Gtl2-DMR* in the placentas of the F1 and F2 generations and affect their gene expression levels, which may result in a reduction in the weight of the placentas of the F1 generation and can be transmitted to the F2 generation through a paternal line[89], indicating that the methylation of key genes in the placenta has potential transgenerational effects on offspring development.

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## **IMPACT ON THE EXPRESSION OF PLACENTAL MIRNAS**

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The upregulation or downregulation of miRNAs in the placenta can regulate the proliferation and infiltration of placental trophoblasts and thus affect placental development and function. Inactivation of the placental miRNA mechanism has an impact on fetal weight and metabolism and may affect fetal growth and development[90].

An experiment with HTR-8/SVneo and BeWo cells reported that high glucose concentrations inhibited cell viability and reduced the expression levels of placental miR-132, which could promote trophoblast cell proliferation and infiltration[91]. In addition, some studies have reported that placental trophoblast proliferation is related to macrosomia. Human and *in vitro* placental experiments have shown that placental weight is closely related to macrosomia in GDM patients, possibly because Erk1/2 signaling is activated by hyperglycemia and promotes trophoblast cell proliferation[92]. Another study also confirmed that the macrosomia of GDM patients is associated with placental trophoblast proliferation[93]. The expression levels of miR-130b-3p, miR-29a-3p, and miR-let-7a-5p in the placenta of GDM patients decreased with increasing birth weight[94]. MiR-508-3p was upregulated in GDM patients, and EGFR/PI3K/Akt signaling was activated by the targeted reduction in PIKfyve, a negative regulator of EGFR (epidermal growth factor receptor), leading to the occurrence of macrosomia[95]. These findings indicate that the placenta alters key miRNAs involved in fetal development to adapt to a maternal intrauterine hyperglycemic environment and plays an important role in fetal development.

miRNAs also participate in placental glucose and lipid metabolism. It has been reported that miR-21 is downregulated in the placenta of GDM patients, whereas the expression of PPAR $\alpha$ [96], a nuclear receptor involved in lipid and glucose homeostasis, is increased. miR-9 and miR-22 are downregulated in the placenta of GDM patients and upregulate the expression of GLUT1 and HK2, leading to increased glucose uptake in primary syncytiotrophoblasts and HTR8/SVneo cells[97]. The downregulation of miR-29b in the placenta of GDM patients promoted trophoblast activity in the placenta and increased glucose uptake by increasing the expression of hypoxia-inducible factor 3 subunit  $\alpha$  (HIF3A)[98]. However, the expression levels of miR-98[99] and miR-199a[100] were significantly increased in the placentas of GDM patients, and these genes indirectly regulated glucose uptake by targeting the *Mecp2-Trpc3* pathway. It has been reported that the expression level of miRNA7 in the placenta of GDM patients increases, and the placental insulin signaling pathway and glucose metabolism are regulated by means of targeted downregulation of IRS1 and IRS2[14]. These results indicate that miRNAs participate in glucose metabolism and insulin signaling alterations in the placentas of GDM patients and may be involved in the pathogenesis of GDM and lead to metabolic disorders in offspring. Therefore, the NRS-2002 can also be used as a useful marker for the diagnosis of GDM.

In conclusion, placental epigenetic modifications play an important regulatory role in the programming of fetal development in patients with GDM and are related to maternal metabolism. Multiple placental epigenetic modifications affect fetal development by regulating placental function, gene expression, fetal weight and fetal metabolism. Understanding the relationship between placental epigenetic changes and fetal development is highly important for revealing the molecular mechanism of fetal development and identifying related diseases. In the future, by means of interfering with placental epigenetic abnormalities, new treatments can be explored to improve fetal development and prevent the occurrence of related diseases.

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## DEFICIENCIES AND PROSPECTS

An intrauterine high-glucose environment alters placental function, epigenetics and gene expression, participates in fetal intrauterine programming, has an important impact on offspring development, and increases the prevalence of obesity, cardiovascular disease and metabolic syndrome in adult offspring. The understanding of the impacts of the placenta on fetal development is insufficient at present, and there is still a long way to go. First, there is a theoretical relationship between placental function and epigenetic abnormalities in GDM patients and fetal development, and there is some supporting evidence to prove their correlation with fetal development. The placenta receives signals from both maternal nutritional reserves and fetal development needs, but the mechanism of integration and the exact nature of these signals and their regulation and influence on a high-glucose environment are still unclear. In the future, further probing of the molecular mechanism and etiology of placental epigenetic changes and their effects on the development of offspring can be performed by means of a molecular pathological epidemiology (MPE)[101] technique, which links potential risk factors with the molecular pathology of diseases and contributes to precision prevention and precision medicine[102], providing a theoretical and scientific basis for early warning, prevention and treatment of GDM. In addition, MPE research can explore the association between GDM and later chronic diseases and other diseases[103], providing new strategies for combined prevention and individualized treatment of diseases. Second, the current research has focused mainly on static analysis of placental function and epigenetics and has lacked observations of dynamic changes. However, the process of fetal development is dynamic, and our study can provide information only on changes at certain time points. To better understand the temporal relationship between placental function and epigenetics and fetal development, long-term follow-up observations are needed to obtain additional comprehensive information. In addition, although the animal models used in the experiments are similar to those used in humans, there are still some differences that prevent direct application of the results to the human placenta. However, further validation combined with human placenta studies is needed.

GDM has a profound impact on the development and subsequent health of offspring. As an intermediary organ between the mother and the fetus, the placenta plays a crucial role, and further investigations of the relationship between MPE changes in the placenta and abnormal fetal development are required to understand the specific mechanism involved in the development of the placenta in offspring and to determine the causal relationship between the placenta and fetal development. Only in this way can we have a deeper understanding of the pathophysiological process of abnormal development in offspring and associate this process with external factors and the development of chronic diseases in the later stage to improve the outcomes of pregnant women with GDM and their offspring.

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## CONCLUSION

In a word, altered placental function and epigenetic modifications in GDM mothers are associated with an increased risk of obesity, metabolic diseases, and cardiovascular diseases in offspring. These changes may affect the metabolic function of offspring and increase disease susceptibility by changing the expression of genes. Therefore, it is important to understand the impact of changes in placental function and epigenetic modifications of the placenta in GDM on offspring development, and to explore how to optimize maternal and infant health by adjusting placental function and epigenetic modifications. In the future, further efforts should be made to explore the biological mechanism of the placenta and placental MPE, so as to develop more effective prevention and treatment measures to ensure the overall health of GDM patients and their offspring.

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## FOOTNOTES

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**Co-corresponding authors:** San-Hong Zhang and Wei Xu.

**Author contributions:** Yi Y and Wang T reviewed and summarized the literature and wrote the paper; Zhang SH and Xu W designed and revised the manuscript; Xu W is the guarantor of this work; all authors were involved in the critical review of the results and have contributed to read and approved the final manuscript; Yi Y and Wang T contributed equally to this work as co-first authors, Zhang SH and Xu W as co-corresponding authors. The reasons for designating Zhang SH and Xu W as co-correspondent authors are threefold. First, the research was performed as a collaborative effort, and the designation of co-corresponding authorship accurately reflects the distribution of responsibilities and burdens associated with the time and effort required to complete the study and the resultant paper.

This also ensures effective communication and management of post-submission matters, ultimately enhancing the paper's quality and reliability. Second, the overall research team encompassed authors with a variety of expertise and skills from different fields, and the designation of co-corresponding authors best reflects this diversity. This also promotes the most comprehensive and in-depth examination of the research topic, ultimately enriching readers' understanding by offering various expert perspectives. Third, Yi Y and Wang T contributed efforts of equal substance throughout the research process. The choice of these researchers as co-first authors acknowledges and respects this equal contribution, while recognizing the spirit of teamwork and collaboration of this study.

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