Chapter

Future Risks for Children Born to Mothers with Gestational Diabetes: Elucidation Using the Cell Model Approach

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Abstract

A number of studies have shown that foetal nutritional status significantly impacts an unborn child’s long-term health. The developmental origins of health and disease (DOHaD) hypothesis proposes that if a child is undernourished in the foetal period, the child will develop diabetes and hypertension in the future if adequate nutrition is given after birth. Moreover, hyperglycaemia (e.g. gestational diabetes mellitus [GDM]) experienced during foetal life can reportedly cause various complications in children. As diabetes is increasing worldwide, so is GDM, and many studies have been conducted using GDM animal models and GDM cell lines. We examined the effects of streptozotocin-induced diabetes, particularly on the heart of offspring, in rat GDM animal models. We also analysed primary cardiomyocyte cultures isolated from these GDM rats and found that insulin signalling was inhibited in GDM cells, as in the GDM animal models, by increased advanced glycation end products. Furthermore, the effect of eicosapentaenoic acid during pregnancy has been reported in GDM animal models and cells, and the findings indicated the importance of nutritional management for GDM during pregnancy.

Keywords: developmental origins of health and disease, fetus, high glucose, hyperglycaemia, advanced glycation end products, eicosapentaenoic acid

1. Introduction

Several studies have shown that foetal nutritional status has a significant impact on an unborn child’s long-term health. Barker et al. found that areas with high neonatal mortality between 1921 and 1925 had higher cardiovascular mortality between 1969 and 1978 [1]. Barker et al. later reported that low birth weight correlated with glucose intolerance and cardiovascular disorders [2, 3]. Furthermore, they also proposed the Barker theory that “prenatal undernutrition increases the risk of lifestyle-related diseases in adulthood” [4]. Later, Gluckman and Hanson proposed the developmental origins of health and disease (DOHaD) hypothesis, which states that predisposition to lifestyle-related diseases is shaped by gene–environment interactions during fertilisation, embryonic development, foetal life, and infancy and that excessive nutrition after birth leads to the development of diabetes and hypertension (Figures 1 and 2) [5, 6].
Figure 1.
Foetal nutritional status has a major impact on postnatal health. It has been shown that even if the mother is undernourished during pregnancy, if the child is well nourished after birth, the child will develop diabetes and metabolic syndrome in the future. This has been defined as the developmental origin of health and disease (DOHaD) hypothesis. By contrast, GDM, an excessive nutrition (high glucose) environment during pregnancy, similarly increases the child’s risk of developing diabetes and metabolic syndrome in the future. Many studies have reported that nutritional status during pregnancy has a significant impact on the health of the child.

Developmental Origins of Health and Disease (DOHaD)

Figure 2.
The diseases envisioned through the developmental origins of health and disease (DOHaD) hypothesis include learning disabilities, schizophrenia, high blood pressure, coronary heart disease, dyslipidemia, decreased renal function, autism spectrum disorders, depression, and type 2 diabetes.
This hypothesis is also supported by many epidemiological studies, which now clearly show that low birth weight increases the risk of developing a diverse array of diseases, such as coronary artery disease, hypertension, stroke, diabetes, obesity, and metabolic syndrome. One example is the findings during the Dutch winter famine, wherein calorie intake had been temporarily lowered to 700 kcal/day for six months in 1944 due to the food embargo in the Netherlands during World War II. Children born during this period exhibited an increased risk of developing various diseases in adulthood, including glucose intolerance, lipid disorders, and ischemic heart disease. Moreover, during the starvation caused by China’s Great Leap Forward policy, those born during this period reportedly had an increased risk of type 2 diabetes and hypertension [7, 8]. Highly accurate and detailed birth record data such as birth weight, postnatal weight, and placental size were recorded at the University of Helsinki Hospital from 1934 to 1944. Barker and his colleagues analysed the records and found that children with low birth weight were more likely to develop myocardial infarction, diabetes, and hypertension, as well as cognitive decline and depression in the future [9–12].

It is very difficult to prove a causal relationship between these foetal intrauterine environmental factors and their effects on the development of postnatal health and illness. However, in recent years, basic research using pregnant animal models as well as cell models are gradually clarifying the underlying molecular mechanism. In this chapter, we will introduce the findings on the effects of overnutrition, as represented by gestational diabetes mellitus (GDM), on animal offspring, rather than discuss findings from the perspective of undernutrition during the foetal period, which has already been extensively studied.

The structure of this paper is as follows: the introduction section describes the DOHaD theory and provides a description on the increasing number of diabetic patients worldwide; Section 2 provides an overview of gestational diabetes; Section 3 describes the use of GDM animal models; Section 4 describes studies using hyperglycaemia cell models; and Section 5 describes the latest research on drug and diet therapy for GDM.

2. Gestational diabetes mellitus

The International Diabetes Federation (IDF) estimates that the global diabetes population continues to increase with 463 million people being pre-diabetic in 2019 with a projected increase of up to 578 million by 2030. In addition, one in six women will develop abnormal glucose metabolism during pregnancy. The IDF has identified women with diabetes as a key challenge, with measures to improve the control of all types of diabetes being needed [13]. The prevalence of type 1 and type 2 diabetes in women of childbearing age is increasing, affecting about 1% of all pregnancies. Prevention is also important because of the increasing costs of diabetes care. Babies with extremely low or high birth weight are at high risk of diabetes [10]; therefore, nutritional management during pregnancy is important. Furthermore, inadequate glycaemic control in early pregnancy is associated with increased rates of congenital malformations, spontaneous abortions, stillbirths, and perinatal mortality [14–18]. It may also be associated with various pregnancy complications as well as neurodevelopmental disorders in the offspring. Similarly, long-term problems in the offspring due to insulin resistance may increase the risk of cardiovascular disease, hypertension, and diabetes mellitus (metabolic syndrome).

GDM is one of the most frequent complications of pregnancy, with an increasing rate [19, 20]. The prevalence of GDM varies in direct proportion to the prevalence of diabetes.
of type 2 diabetes and is higher among Hispanic, African American, Native American, Asian or Pacific Islander, and South Mediterranean women [21, 22]. It also varies by maternal age and diagnostic criteria [23, 24]. Since 2010, the international Association for the Study of Diabetes and Pregnancy (IADPSG) has tightened the criteria for the diagnosis of GDM, based on the 2008 Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study [25]. The reason for this was that the HAPO study reported a higher risk of macrosomia in newborn born to mothers with high blood glucose levels, even though GDM was not diagnosed using the previous criteria [26]. As a result, many GDM patients have been identified. The HAPO study was a large observational study of approximately 25,000 pregnant women with impaired glucose tolerance conducted in 15 centres across 9 countries; the correlation between blood glucose levels was examined at 24–32 weeks’ gestation with various pregnancy complications [27]. The endpoints of the diagnostic criteria for GDM were perinatal factors (heavy-for-dates infants, first caesarean section, neonatal hypoglycaemia, and hyperinsulinemia in the infant). The results showed that these perinatal complications were significantly associated with maternal blood glucose levels, even after adjusting for confounding factors such as maternal obesity. Furthermore, many epidemiological studies have shown that children born with GDM are associated with future development of noncommunicable diseases (NCDs) such as obesity and diabetes. Clausen et al. reported that the hyperglycaemic environment in utero and genetic background are associated with the future development of diabetes in children [28]. Sugihara et al. reported that infants born with macrosomia were also associated with childhood diabetes compared with low and normal birth weight [29].

Maternal undernutrition as well as GDM in an overnutrition environment are associated with the development of NCDs in future infants, indicating the importance of nutritional management during pregnancy (Figures 3 and 4) [29].

**Effect of Hyperglycemia on the Fetus**

**Gestational Diabetic Mother (GDM)**

- **Mother’s Hyperglycaemia**
- **Placenta**
- **Mother’s Insulin**

**Infant of GDM**

- **Fetal Hyperglycaemia**
- **Impaired glucose tolerance**
- **Macrosomia hypoglycaemia**

*Figure 3.* Similar to GDM, if the mother is hyperglycaemic, the foetus becomes exposed to hyperglycaemia. If hyperglycaemia persists, the foetus will develop insulin resistance and complications such as macrosomia and hypoglycaemia.
3. Animal model for gestational diabetes mellitus

Diabetes in pregnancy increases the risk of various complications for both the mother and the child. However, the pathogenesis of GDM and its molecular mechanisms have not yet been fully elucidated. Animal and cell models are mainly used in basic research regarding GDM. GDM animal models play a major role in elucidating the pathogenesis and pathophysiology of diabetes, as well as elucidating the mechanisms of its complications. They also provide the theoretical basis for early detection and prevention of GDM and the subsequent clinical dosing and drug evaluation. Diabetes mellitus in humans is associated with complications such as peripheral neuropathy, nephropathy, and retinopathy in about 50% of cases, but there are few animal models that develop all complications; moreover, the animal models are selected according to the research purpose. The most widely used species for diabetes animal models are the mouse and rat. The animal models for type 1 diabetes range from animals that spontaneously develop autoimmune diabetes to those that chemically destroy pancreatic beta cells.

3.1 Spontaneous diabetic models

Spontaneous diabetic animals are not only produced by natural or selective breeding, but also by introducing genes from wild mice. The non-obese diabetic (NOD) mouse and bio breeding (BB) rat are the two most commonly used animals that spontaneously develop diseases similar to human type 1 diabetes. The NOD mouse was established by Makino et al. in the Shionogi Laboratory [30]. The BB rat was discovered in a commercial colony of Wistar-derived rats at the Bio-Breeding Laboratories in Ottawa, Canada [31].

The Goto-Kakizaki (GK) rat was established by Goto and Kakizaki as a non-obese, hypoinsulinemic model of type 2 diabetes [32]. GK rats are a diabetes model mainly due to their trait of non-obesity insulin deficiency established as in an inbred line by selective mating from Wistar rats using impaired glucose tolerance [33]. The Spontaneously Diabetic Torii (SDT) rats were established through inbreeding by selecting and mating Sprague–Dawley rats who developed

![Complication of GDM](image)
diabetes [34]. The SDT rat is a novel model of type 2 diabetes that is non-obese, has hypoinsulinemic diabetes, and is characterised by the presence of diabetic retinopathy in individuals with prolonged hyperglycaemia [35]. Diabetes is prominent in males of this model, with diabetes occurring in almost 100% of males at 40 weeks. SDT rats develop proliferative retinopathy and are used as a model for human diabetic retinopathy [36].

3.2 Obese type 2 diabetes model animals

Spontaneous obesity-diabetes models (ob/ob mice, OLETF rat, KK and KKA mice, TSOD mice, SMXA5 mice, and Kuma mice) can be analysed for physiological, biochemical, and pathological changes during the onset and progression of type 2 diabetes [37].

Ob/ob mice exhibit prominent overeating, are obese at 2 weeks of age, and reach a body weight of 40 g at 6 weeks and 60 g at 14 weeks. Later, in addition to overeating and obesity, the mice exhibit hyperglycaemia, hyperinsulinemia, and high blood glucagon levels. Insulin resistance is observed in the peripheral tissues and the liver.

Otsuka Long-Evans Tokushima Fatty (OLETF) rats were established as inbreeding strains through the selective mating of diabetes-developing individuals found in Long-Evans rats. Binge eating obesity is exhibited immediately after weaning, and urinary sugar appears from 40 weeks after birth. Diabetes onset is prominent in males [38].

The KK mouse was established as an inbreeding strain from the experimental mouse produced in the Kasukabe region of the Saitama prefecture in Japan and was named KK mouse after Kasukabe [39]. KK mice are dominated by many diabetic genes, but their pathology is mild. Therefore, the KK-Ay mice were created, wherein the naturally mutated obesity gene, Ay, was introduced [40].

KK-Ay mice develop severe obesity and hyperglycaemia 7–8 weeks earlier than KK mice. The incidence of diabetes in males is approximately 100%. Nagoya-Shibata-Yoshida (NSY) mice were established as inbreeding strains by selecting and mating ICR mice with impaired glucose tolerance. Impaired glucose tolerance and elevated blood glucose are exhibited after 8 weeks, and impaired glucose tolerance occurs in almost 100% of males at 48 weeks [41].

Tsumura Suzuki Obese Diabetes (TSOD) mice were established as inbreeding strains by selecting and mating ddY mice, which are highly reproductive non-inbred mice, exhibiting urinary sugar and obesity. During the growth period of 4 to 20 weeks of age, strong overeating is observed, and obesity is exhibited; moreover, hyperglycaemia and abnormal lipid metabolism due to insulin resistance are likewise exhibited. The symptoms are strongly expressed in males [42].

SMXA5 mice are SMXA mice with recombinant inbreeding strains, as well as a high-fat diet-induced type 2 diabetes and fatty liver [43]. Impaired glucose tolerance and hyperinsulinemia frequently develop from 10 weeks of age. For Kuma mice, genome editing technology was used to obtain mice lacking glutamine, the 104th amino acid of the insulin 2 protein, from the immunodeficiency model BRJ mice [44]. This mouse has elevated blood glucose levels after 4 weeks of age.

3.3 Animal model of chemistry-induced diabetes mellitus

Type 1 and type 2 diabetes models can be created by destroying islet of Langerhans cells in the pancreas through drug administration. The main advantages of this method are its relative ease in inducing a model of diabetes, not requiring the use of a specific strain, and the short development time. Most of these animals have type 1 diabetes, but depending on how the drugs are administered, models similar
to type 2 diabetes can also be created. The drugs used are streptozotocin (STZ) or alloxan (Alx). STZ is a nitrosourea derivative isolated from *Streptomyces achromo-
gen* [45]. Drug-induced diabetic rats can also be created from mature rats by intra-
venous administration of 30 mg/kg STZ or 40 mg/kg Alx. STZ administration to adult rats will produce a type 1 diabetic model, and administration to neonates will produce a type 2 diabetic-like model. Induction is usually done in early pregnancy, before the foetal pancreas has developed, to avoid foetal beta cell destruction by the chemicals being utilised. Alx can create a diabetes model by generating reactive oxygen species (ROS) in the beta cells of the pancreas and destroying these cells.

### 3.4 Surgically-induced models

Surgical models of diabetes were first created through canine pancreatectomy. In particular, GDM models were created through canine pancreatectomy at various stages of gestation [46]. The disadvantage of this model is that it lacks specificity, as both endocrine and exocrine tissues are removed, causing other symptoms not associated with diabetes mellitus. This is a model of GDM due to insulin deficiency, and not insulin resistance [46]. As mentioned above, there are spontaneous animal models and transgenic animal models of diabetes, but most of them often show remarkable symptoms in males. Since the pregnancy and childbirth of hypergly-
caemic mothers are often difficult, the effects of the intrauterine hyperglycaemic environment on children cannot be observed. Thus, we used chemical virulence factors to cause specific damage to the beta cells in the pregnant animal’s pancreas, inducing complications similar to GDM. Therefore, we obtained the offspring from the GDM animal model by mating normal Wistar rats and then administering STZ to the tail vein, rather than using diabetic model rats.

### 4. Intrauterine hyperglycaemia-mimicking cell model

In the case of GDM, foetation is exposed to maternal hyperglycaemia through the placenta during the foetal period. The DOHaD study described in the Introduction mainly focused on the effects of inadequate nutrition during the foetal period (intra-
uterine undernutrition environment) on the future development of disease in the offspring [4–6]. When the womb provides over-nutrition, the offspring will exhibit numerous complications, as previously described. Recently, studies have been conducted that mimic the hyperglycaemic environment by changing the glucose concentration in the medium using primary cultured cells and cell lines. Nerve cells and skeletal muscle cells, among others, in which cells differentiate and their fate is determined during the foetal period, are important. Although it is possible to use primary cultured cells isolated from foetal organs for these studies, the experiments may be limited because the differentiated cells do not proliferate. Therefore, by using a cell line, the cells can be handled more easily than primary cells.

Myocardial blasts established from rats are often used as heart model cells [47]. The exposure of H9C2 cells to Dulbecco’s modified Eagle’s medium containing 50 mM high glucose was compared with a medium containing 5.5 mM glucose (the normoglycemic level), and the H9C2 cells reportedly exhibited apoptosis in the high glucose medium [48]. Another study with H9C2 cells showed that simvastatin has an autophagy-mediated cardioprotective effect; this study used a cell model wherein exposure to 200 mM high glucose induced cardiomyocyte apoptosis [49]. Studies using these myocardial blast cell lines suggest that high glucose in an intra-
uterine hyperglycaemic environment has a profound effect on foetal myocardial blast signalling and proliferation.
PC12 cells, which are pheochromocytoma cells derived from the adrenal gland of *Rattus norvegicus*, are often used in the study of nerve cells [50]. PC12 cells can be differentiated using the nerve growth factor (NGF) to investigate the effects on neurons [51]. Furthermore, high glucose has been shown to cause oxidative stress-induced apoptosis in dopaminergic neurons. Studies with PC-12 cells revealed a correlation between hyperglycaemia and neurodegeneration using a PC-12 cell model exposed in a high glucose medium. Resveratrol, a polyphenol contained in red wine, suppresses nerve cell death due to apoptosis induced by a high glucose environment [52]. Similar studies have been conducted on PC12 cells, indicating that resveratrol or alpha-lipoic acid protected PC12 cells from HG-induced oxidative stress and apoptosis through activation of the PI3K/Akt/FoxO3a signalling pathway [53, 54]. These results suggest that the intrauterine hyperglycaemic environment during pregnancy may lead to inflammation and apoptosis of foetal neurons due to long-term exposure to foetal hyperglycaemia.

Next, we present a study of the effects of high glucose on cells in a skeletal muscle cell model of GDM. Skeletal muscle is an essential organ for energy metabolism. During foetal development, myoblasts differentiate into skeletal muscle during development. Several cell-level studies on how the hyperglycaemic environment affects the differentiation of myoblasts into skeletal muscle are being conducted. In a cell model using mouse myoblasts C2C12, high glucose exposure of 25 mM was shown to accelerate myogenesis by rearranging SUMO enzyme transcripts and SUMO proteins [55]. However, other experiments with C2C12 have shown that even higher glucose concentrations of 60 mM inhibit the expression of the MyoD and myogenin genes, as well as the Akt signal, suppressing skeletal muscle differentiation [56]. High glucose was also shown to interfere with the proliferation of muscle-specific stem cells and satellite cells under adherent culture conditions [57]. Therefore, it is suggested that hyperglycaemia may promote sarcopenia. Glucose is also suggested to be a factor that determines the cell fate of skeletal muscle-specific stem cells. Recently, we found that high glucose (25 mM) in the medium increases the expression of skeletal muscle differentiation marker genes such as MyoD and myogenin compared to normal glucose levels (5 mM), resulting in ROS development and Akt signalling. The differentiation of myoblasts into skeletal muscle was reportedly promoted by high glucose [55]. The appearance of unusually large babies with gestational diabetes complications may be due in part to excessive muscle differentiation.

5. Our study on intrauterine hyperglycaemia

While there have been many studies using animal and cellular models of GDM, few studies have analysed the effects of GDM on the pups born from it. We have previously studied the effects of STZ-induced GDM on the heart of pups using a rat model of GDM. In this section, we describe (1) the effects of a high-fat diet during pregnancy on the hearts of GDM rat pups, (2) the effects of fish oil intake during pregnancy on the hearts of GDM rat pups, and (3) the effects of eicosapentaenoic acid (EPA) intake during pregnancy on primary cardiomyocyte cultures isolated from GDM rat pups.

5.1 Effect of a high-fat diet on stillbirth rate during pregnancy in GDM model rats

GDM model rats were created by administering STZ (50 mg/kg) into the tail vein of Wistar rats on the second day of pregnancy. To investigate the effect of a high-fat
diet during pregnancy on the pups, GDM rats were fed a high-fat lard diet (56.7% fat) containing saturated fatty acids and a control diet (7% fat). The stillbirth rate of GDM rats on the high-fat lard diet was much higher than that of GDM on the control diet [58]. Palmitic acid, a saturated fatty acid, has been reported to cause inflammation and cardiac dysfunction in animal and cellular level experiments [59]. In addition to exposure to hyperglycaemia in utero, the consumption of a high-fat lard diet high in saturated fatty acids may have impaired cardiac function in the pups.

5.2 Effect of fish oil intake on the heart of rat pups in the GDM model

In this study, we examined the effects of fish oil (which is rich in ω3 unsaturated fatty acids) on pups, based on reports that fish oil has a positive effect on cardiovascular diseases [60, 61]. GDM rats were fed a high-fat fish oil diet (14% fish oil + 7% lard), a high-fat lard diet rich in saturated fatty acids (21% lard), and a normal diet (7% lard), and the heart signals of the pups were then analysed. The pups of GDM rats fed the lard diet had higher stillbirth rates and triglyceride levels, but these were improved in the pups fed the fish oil diet [62]. An examination of Akt-related signalling revealed that pups born to GDM rats fed a lard diet had reduced levels of Akt phosphorylation, which is important for sugar uptake. Interestingly, however, these signalling abnormalities were ameliorated in the hearts of pups born to GDM rats fed a fish oil diet during pregnancy.

5.3 Effect of EPA intake on primary cardiomyocytes of rat pups in the GDM rat model

Our results indicate that intrauterine hyperglycaemia induces abnormal insulin signalling in the foetal heart. Why does abnormal heart signalling occur...
in the pups? What components of fish oil can be ingested by pregnant mothers to improve the condition? Fish oil is a rich source of the n-3 unsaturated fatty acids EPA and DHA. EPA was chosen as a candidate because it has cardiovascular protective properties, and DHA is biosynthesised by the body from EPA. GDM rats were orally administered EPA through gavage during pregnancy. Primary cardiomyocyte cultures isolated from the hearts of the pups were examined for effects on the insulin signalling system [63]. We found that the inhibition of insulin signalling in primary cardiomyocyte cultures from GDM rats inhibited the translocation of GLUT4 to the plasma membrane. Why do these signalling abnormalities occur? In cultured primary cardiomyocytes from GDM rats, ROS was generated and an increase in excessive protein advanced glycation end products (AGEs) was observed. This AGEsation has been highlighted as a cause of ageing and disease. The accumulation of AGEsed proteins also increases the expression of the receptor of AGEs (RAGE), which triggers AGEs-RAGE signalling. This AGEs-RAGE signalling was found to increase various pro-inflammatory cytokine genes (IL-6, TNFα, and NF-κB) through JNK phosphorylation (Figure 5). These results indicate that exposure to hyperglycaemia in the foetus of GDM rats leads to increased AGEs oxidation and chronic inflammation. However, GDM rats fed EPA (an ω3 unsaturated fatty acid) during pregnancy were shown to ameliorate the abnormalities in the pups.

6. Diet and drug therapy for GDM

What other drugs are effective against GDM besides insulin? The effect of using metformin and insulin on GDM has already been reported [64]. Metformin is associated with a decreased incidence of GDM [65]. The weight of metformin-treated neonates is lower than that of insulin-treated neonates. In addition, metformin-treated infants had lower rates of weight gain and malformations during pregnancy than insulin-treated infants. In contrast, metformin-treated infants had greater weight gain in the neonatal period, with no difference in weight between those administered with insulin and metformin. This suggests that weight gain during this period may be linked to cardiovascular disease and indicates the need for additional research. We have previously investigated dietary treatment in GDM rats. EPA, an n-3 unsaturated fatty acid, was administered to GDM rats from day 1 to day 22 of gestation and the effect on new-born rats was investigated. In the heart of puppies born to GDM rats, excessive AGE formation of cardiac proteins impaired signal transduction, but feeding EPA to GDM rats inhibited AGE formation and improved signal transduction. Since AGE is the cause of various diseases [65], several drugs have been developed to inhibit AGEs. The accumulation of AGEs has been reported to induce inflammation and damage vascular endothelial cells, smooth muscle cells, and fibroblasts [66]. In addition to diabetes mellitus, other diseases wherein AGEs are involved include neurodegenerative diseases, cardiovascular diseases, chronic renal failure, and autoimmune diseases [67]. AGE formation inhibitors, AGE destroyers, AGEs-RAGE inhibitors, and signal transduction inhibitors have been previously reported [68–72]. For example, studies on AGE formation inhibitors found that some amino acids in the plasma inhibit glycation by competitively inhibiting the molecular binding of glucose to proteins [73]. Furthermore, AGE-RAGE inhibitors have been shown through animal studies to be protective against diabetic nephropathy when DPP4 is deficient or when DPP4 inhibitors are added [74].
7. Conclusion

Undernutrition or overnutrition during pregnancy has profound effects not only on the mother but also on the child. Children with GDM are focused on neonatal complications, but in the future, they may suffer from lifestyle-related and mental illnesses. Elucidation of these molecular mechanisms is becoming clear using animal models and cell models. Thus, GDM has a major impact on the mother as well as on the child and should be treated rigorously with medication and diet. Insulin is the main drug therapy for controlling blood glucose, but in addition to insulin, insulin resistance improving drugs such as metformin have been tried, but the safety is still unknown. Therefore, dietary management is essential for GDM in addition to safe medication.

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Conflict of interest

The authors declare no conflict of interest.

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