# Effect of Gestational Diabetes Mellitus on Pancreatic Development in Offspring

## Yang Huimin[1,a], Mi Yang[2,b,*]

*[1]The Second Clinical Medical College, Shaanxi University of Chinese Medicine, Xianyang, Shaanxi, 712046, China*
*[2]Department of Gynaecology and Obstetrics, Northwest Women's and Children's Hospital, Xi'an, Shaanxi, 710061, China*
*[a]2245630934@qq.com, [b]miyangmm@163.com*
*[*]Corresponding author*

*Abstract:* Gestational diabetes mellitus (GDM) is one of the most common complications during pregnancy, which not only increases the incidence of adverse pregnancy outcomes but also affects the long-term quality of life for both the mother and child. Offspring of GDM display impaired insulin secretion and disrupted glucose metabolism, significantly increasing the risk of developing type 2 diabetes. The pancreas plays a key role in regulating blood glucose homeostasis, and the developmental and functional disturbances of the pancreas in GDM offspring are closely related to the occurrence of metabolic diseases. This review summarizes the changes in morphology, structure, and function of the pancreas in GDM offspring, as well as the underlying mechanisms. The aim is to provide researchers with a better understanding of the pathophysiological mechanisms related to impaired pancreatic development in GDM, and to establish a theoretical basis and new perspectives for the prevention and management of GDM and the health of its offspring.

## 1. Introduction

Gestational diabetes mellitus (GDM) is a transient hyperglycemia caused by insulin resistance and impaired pancreatic β-cell function during pregnancy. Globally, the standardized prevalence rate of GDM in 2021 was 14%, with the Western Pacific region having a rate of 14.7% [1]. In China, the incidence of GDM has sharply increased in the past decade, growing from 4% in 2010 to 21% in 2020 [2]. GDM is one of the most common complications during pregnancy, not only increasing the occurrence of adverse pregnancy outcomes such as gestational hypertension, preeclampsia, preterm birth, macrosomia, birth trauma, cesarean section rate, and neonatal intensive care unit admission, but also affecting the long-term health quality of both mother and child [3]. The beginning of life is crucial. Even if GDM-related hyperglycemia occurs after the organogenesis window, the risk of congenital heart defects, craniofacial abnormalities, digestive system abnormalities, genitourinary system abnormalities, and skeletal muscle system abnormalities in GDM offspring will increase [4]. The intrauterine hyperglycemic environment can disrupt normal fetal development patterns and potentially permanently alter body structure and physiological metabolism, thus predisposing to

chronic diseases such as obesity and type 2 diabetes mellitus (T2DM) [5].

The pancreas, located behind the peritoneum, is a dual-function gland with endocrine and exocrine functions, playing a crucial role in maintaining blood glucose homeostasis. Pancreatic abnormalities can impair both endocrine and exocrine functions, leading to glucose metabolism disorders and increased risks of obesity and T2DM. Compared to non-diabetic individuals, those with T2DM have increased amyloid deposition in pancreatic tissue, inhibited β-cell proliferation, increased apoptosis, and a 40%-60% reduction in β-cell numbers and insulin content [6]. In the development of T2DM, β-cell dysfunction plays a more important role than β-cell loss [7], with the molecular mechanisms of β-cell damage mainly involving endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, autophagy, and inflammation [8]. In mammals, fetal pancreatic β-cells in late pregnancy already possess a basic insulin secretory capacity and gradually develop to reach the adult level after birth [9]. However, even transient exposure to a hyperglycemic environment during pregnancy can affect pancreatic development in offspring and increase the risk of glucose metabolism disorders [10]. Therefore, this review elucidates the impact and mechanisms of GDM on the development and function of offspring pancreatic, aiming to provide a theoretical basis and new perspectives for the prevention and management of GDM and the health management of its offspring.

## 2. Changes of pancreatic morphology and function in GDM offspring

The pancreas is divided into three parts: the head, body, and tail. The tail of the pancreas contains clusters of cells called islets, which make up the endocrine gland of the pancreas. The islets mainly consist of alpha cells and beta cells, which secrete glucagon and insulin, respectively. Insulin is the only hypoglycemic hormone in the body, and its dysregulation leads to imbalanced blood glucose regulation, resulting in glucose metabolism disorders and increased risk of obesity and T2DM. Therefore, changes in the structure and function of pancreatic tissue severely impact the overall health of the body.

Due to anatomical and ethical limitations, studies on the structure and function of the pancreas in offspring of GDM are mostly conducted using animal models. Obesity is a high-risk factor for GDM, so researchers often use a high-fat diet to create GDM animal models. In non-human primates [11-13], it has been observed that in the fetal stage (130 days of gestation), there is no difference in pancreatic weight and islet number compared to the control group, but there is a decrease in the number of smaller islets. Although no changes in the number of pancreatic beta cells have been observed, a decrease in the number of alpha cells has been found, indicating an increased insulin secretion in response to glucose stimulation in the pancreas, which persists until 3 years of age. After weaning, both the control group and GDM offspring were subjected to a high-fat diet induction, and at the age of 1 year, it was found that the control group had increased numbers of islets, alpha cells, and beta cells, while the islets in GDM offspring were enlarged with only an increase in beta cell numbers. In rodent studies [14,15], there were no changes in the number of newborn islets, but the shape of the islets was larger and more irregular, with a decrease in beta cell numbers but an increase in alpha cell numbers. Although the changes in islet morphology did not persist until 15 weeks of age, impaired glucose-stimulated insulin secretion function and reduced basal insulin secretion were observed, resulting in mild hyperglycemia in the offspring. After weaning, both groups were given a high-fat diet induction until 15 weeks, and it was observed that the control group had an increase in islet area and number, while no similar compensatory response was observed in the GDM offspring's pancreas. The different changes in pancreatic morphology, structure, and function observed in the above studies may be related to the maternal blood glucose levels during the construction of the animal models. Mild hyperglycemia leads to impaired insulin secretion function in adult offspring, while severe hyperglycemia leads to hyperfunction of insulin secretion in adult offspring [16].

Clinical studies have also found impaired glucose tolerance and beta cell dysfunction in offspring of GDM mothers during adulthood [17]. Scholtens et al. followed 4832 children aged 10-14 years and found that maternal hyperglycemia during pregnancy was associated with higher glucose levels and insulin resistance in childhood [18].

In addition, the islets of the pancreas are highly vascularized organs, with dense capillaries playing a crucial role in sensing blood glucose levels and responding to changes in glucose levels, as well as promoting normal pancreatic development [19]. Offspring of GDM mothers show a significant reduction in pancreatic capillary area and density during fetal development, with impaired ability to expand blood vessels in response to metabolic demands [20]. Furthermore, intrauterine exposure to GDM also leads to damage to the ultrastructure of pancreatic beta cells in the offspring, with lipid deposition and endoplasmic reticulum swelling observed in newborn and adult pancreatic beta cells, as well as an increase in mitochondrial quantity [21]. Similar changes have also been observed in the pancreas of individuals with T2DM [22]. Overall, exposure to GDM during pregnancy results in structural and functional damage to the pancreatic morphology in the offspring.

## 3. Effects of intrauterine exposure of GDM on pancreas β Mechanism of cell injury

Insulin synthesis and secretion are carried out in pancreatic beta cells. The insulin gene (insulin) located in the beta cell nucleus is transcribed to generate mRNA, which is then transferred to the endoplasmic reticulum in the cytoplasm for translation, resulting in preproinsulin. Preproinsulin is proteolytically cleaved to form proinsulin, which is then transported via vesicles in the cytoplasm to the Golgi apparatus. Subsequently, the C-peptide is cleaved off by proteolytic enzymes to generate insulin, which is stored in insulin granules in the cytoplasm. Beta cells uptake glucose through glucose transporter 2 (GLUT2), undergo oxidative respiration in the mitochondria, producing a large amount of ATP. This leads to the closure of ATP-sensitive K+ channels on the cell membrane, opening of ATP-sensitive Ca2+ channels, and an increase in intracellular Ca2+ concentration, triggering exocytosis of insulin granules and subsequent release of insulin. Studies have shown that intrauterine exposure to GDM can impair the synthesis and secretion of insulin in pancreatic beta cells, leading to disturbances in glucose metabolism in the offspring, through mechanisms involving endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, inflammation, and altered exocytosis.

### 3.1. Endoplasmic reticulum stress

When the endoplasmic reticulum (ER) is exposed to exogenous or endogenous stimuli, it can lead to the accumulation of misfolded and unfolded proteins in the ER, a pathological condition known as ER stress. Cells have the ability to sense the accumulation of misfolded or unfolded proteins in the ER and typically mitigate ER stress through three classical unfolded protein response (UPR) pathways - the Ire1 pathway, PERK pathway, and ATF6 pathway - to maintain cellular homeostasis. However, prolonged ER stress can trigger programmed cell death. Insulin synthesis is highly dependent on the ER, where proinsulin is folded into its stable 3D conformation, connecting the A-chain and B-chain domains through disulfide bonds. Pancreatic beta cells are also susceptible to ER stress, especially in insulin-resistant states. Studies by Gao et al. and Carroll et al. provide evidence of ER stress in the pancreatic beta cells of offspring exposed to gestational diabetes mellitus (GDM), with evidence of ER swelling and increased expression of ER stress markers (DDIT3, ATF6, HSPA5). Current evidence suggests that ER stress plays a crucial role in the pathogenesis of diabetes, as evidenced by increased expression of ER stress markers in the islets of T2DM patients. Obesity is a high-risk factor for GDM, and related studies have indicated that maternal obesity can impact the ER homeostasis in offspring. In mice offspring induced by a high-fat diet, insulin levels were decreased, and upstream and downstream regulators of the PERK, Ire1, and ATF6 pathways (such as Eif2α, XBP1, EDEM, HERP, ATF4, CHOP) were affected to varying degrees.

## 3.2. Oxidative stress and mitochondrial dysfunction

Mitochondria are responsible for generating a large amount of ATP through energy metabolism, but they also generate reactive oxygen species (ROS). Under normal physiological conditions, intracellular ROS can act as intracellular signaling molecules to regulate normal physiological functions. However, under stress conditions, an imbalance between the generation of ROS and cellular antioxidant defense systems leads to oxidative stress. Previous studies have shown that the pancreas has weak antioxidant capacity, suggesting that it may be more susceptible to oxidative stress compared to other tissues [25]. The current mainstream view is that beta cell damage in the offspring of diabetes is mainly caused by increased ROS. Erisson et al. have shown that ROS plays an important role in high glucose-induced embryonic diseases, and pancreatic beta cells are more sensitive to ROS than other cells [26,27]. Mice given a high-fat diet during pregnancy showed increased ROS generation in pancreatic beta cells, and the expression levels of the antioxidant enzyme gene SOD2 in females increased [28]. Similar observations of increased expression levels of antioxidant enzyme genes SOD2 and NQO1 have also been made in primates. Metabolomic analysis of the pancreas in elderly offspring of GDM has shown that various metabolites and metabolic pathways are associated with ROS. Metabolites that promote oxidative stress, such as L-valine and ceramides, increased in the pancreatic offspring, while metabolites that counteract oxidative stress, such as resveratrol, trimethylselenonium, and biotin, decreased in the pancreatic offspring. Glutathione (GSH), synthesized from cysteine, has been shown to be an essential intracellular antioxidant, and fetal pancreatic cysteine deficiency caused by intrauterine hyperglycemia can lower GSH levels, leading to cellular reactive oxidative stress and dysfunction [29].

Oxidative stress also directly damages mitochondrial function and integrity. Previous studies have found that increased expression of ATP synthase in the pancreas of GDM offspring may be an adaptive response to elevated intrauterine glucose levels [12,14]. Another study found that offspring mice of obese mothers had increased mitochondrial number, area, and density, as well as increased expression levels of mitochondrial respiratory complexes I-IV [28]. Furthermore, Agarwal et al. observed increased expression of 18 different genes encoding ribosomal proteins [14], and ribosome biogenesis occurs concurrently with ER stress [30]. In summary, intrauterine exposure to GDM mediates oxidative stress and mitochondrial dysfunction in pancreatic cells of the offspring.

## 3.3. Inflammatory infiltration

In T2DM, saturated fatty acids directly or through ER stress and oxidative stress trigger inflammation in pancreatic beta cells [8], and inflammatory responses have also been observed in the pancreatic offspring of GDM. In the pancreatic tissue of GDM offspring, elevated levels of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-1α, and IL-6 have been observed, while the anti-inflammatory cytokine IL-10 is decreased [21]. Similarly, Agarwal et al. also confirmed the occurrence of inflammation in the pancreatic offspring of GDM [14]. Among them, IL-1β inhibits beta cell function and promotes Fas-triggered cell apoptosis through the activation of the transcription factor NF-κB [31]. Overexpression of insulin-like growth factor 2 (IGF2) can protect beta cells from IL-1β-induced cell apoptosis, while the expression level of IGF2 is decreased in the pancreatic offspring of GDM [32,33]. Inflammatory infiltration in the pancreatic tissue of GDM offspring is one of the causes of functional impairment.

## 3.4. Pancreas β Imbalance of cell exocytosis

The glucose transporter 2 (GLUT2), located on the cell membrane, has characteristics of low affinity and high capacity for glucose transport, allowing it to transport glucose rapidly regardless of extracellular glucose levels. Glucose metabolism through glycolysis, which produces ATP, alters the state of $K^+$ and $Ca^{2+}$ channels on the cell membrane, leading to an increase in intracellular $Ca^{2+}$

concentration and promoting insulin secretion. Exposure to GDM impairs glucose uptake and the expression of K+ and Ca2+ channels related to insulin exocytosis in the offspring's pancreas. In a study on primates, Japanese macaques that were exposed to a Western diet during pregnancy did not show an increase in insulin vesicle quantity in their pancreatic beta cells at 1 year of age. However, they did exhibit increased expression of the GLUC2 gene and the genes encoding L-type calcium channels (CACNA1C/CACNA1D) and ATP-sensitive potassium ion channel subunits (KCNJ11/ABCC8) [12]. Although an increase in potassium ions inhibits insulin secretion, correlation analysis with insulin area under the curve (IAUC) indicates that calcium ion channels are closely associated with increased insulin secretion. This finding also corresponds to the increased insulin secretion observed in vitro in response to high glucose stimulation in the pancreatic tissue. However, no similar changes were observed in the offspring before weaning. In a study using rodents, 20-week-old offspring of GDM mice showed decreased mRNA and protein expression levels of potassium and calcium ion channels (cav1.3, cav2.3, abcc8), which was associated with increased methylation levels. Insulin treatment during pregnancy did not reverse this damage [29]. Agarwal et al. sequenced the pancreatic tissue of adult offspring of GDM mice at 15 weeks of age and found downregulation of genes related to glucose transporter (GLUT2) and insulin vesicle exocytosis (Vamp2, Snap25, Stxbp1, Gjd2) [14]. Kir6.2 is another subunit of the ATP-sensitive potassium channel on the cell membrane, and in pancreatic beta cells, the kir6.2 (kcnj11) subunit is an important regulator of insulin secretion. It was found that prenatal exposure to GDM reduced the methylation levels of CDKN2A and CDKN2B in the offspring, resulting in downregulation of KIR6.2 expression through the downregulation of the CDK4-pRB-E2F1 pathway and impaired insulin secretion [34,35]. In conclusion, pancreatic beta cells in the offspring of GDM do not show functional impairments in early childhood. However, increased glucose sensitivity and exocytosis lead to increased insulin secretion, eventually resulting in impaired beta cell function and insulin resistance in peripheral tissues in adult offspring.

## 4. The effect of metformin in the treatment of GDM on the pancreas of the offspring of gestational diabetes mellitus

The main treatment methods for gestational diabetes mellitus (GDM) are dietary management, exercise management, and medication therapy. When diet and exercise management are not effective in controlling blood glucose levels during pregnancy, medication therapy becomes the preferred choice. Insulin is the first-line medication for GDM treatment, but if there are reasons to avoid using insulin, metformin is recommended to control blood glucose levels during pregnancy. Compared to insulin, metformin can reach the fetus through the organic cation transporter (OCT) in the placenta, so its safety and efficacy for pancreatic development need further investigation. Animal studies have shown that female mice exposed to a high-fat and high-sugar diet before and during pregnancy had improved glucose tolerance when exposed to metformin in the uterus [36]. Compared to the offspring of GDM mice treated with insulin, the pancreatic ducts of the fetal mice in the metformin group were more regular. Exposure to metformin during lactation also had long-term effects, with increased glucose-stimulated insulin secretion and improved glucose tolerance in male offspring only [37]. These animal experiments suggest that the offspring of mothers with metabolic disorders have more regular pancreatic morphology with better secretory capacity to counteract the damage from a high-fat and high-sugar diet when treated with metformin. However, the long-term effects of maternal exposure to metformin on the offspring's pancreas are still controversial when the mothers are healthy. In in vitro cell experiments [38], metformin intervention during embryonic stem cell differentiation into pancreatic beta cells, in the absence of metabolic disorders, had adverse effects on the development of pancreatic beta cells, regardless of whether metformin was given from the start of differentiation or on the 13th/20th day of differentiation. RNA-seq analysis of the embryonic stem cells at day 35 of differentiation revealed downregulation of genes involved in insulin synthesis, transport, and secretion, upregulation of certain specific mitochondrial genes, and a reduction in net

respiration of pancreatic beta cells. This indicates that in vitro exposure to metformin has detrimental effects on pancreatic development by affecting gene programming. These in vitro experiments cannot fully simulate the uterine environment, as the in vivo environment is more dynamic. Metformin can be cleared through the mother's liver and kidneys, and its clearance rate varies with gestational age, so we need to pay more attention to the local concentration of metformin in fetal tissues in our studies.

## 5. Conclusion

Gestational diabetes mellitus (GDM) not only affects the mother's metabolism and increases the incidence of adverse pregnancy outcomes but also directly influences fetal development and alters the growth trajectory of the offspring. Offspring of GDM mothers exhibit impaired insulin secretion and insulin resistance, which become more pronounced with age. Impaired insulin secretion is related to abnormal development of pancreatic beta cells. The intrauterine hyperglycemic environment in GDM can damage the synthesis and secretion function of pancreatic cells through mechanisms such as endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction, inflammation, and changes in exocytosis. Due to anatomical and ethical limitations, studying the fetal pancreas poses challenges, and long-term follow-up is necessary to validate experimental observations for the benefit of managing the health of GDM offspring and preventing the vicious cycle of metabolic disorders.

## References

[1] Wang Hui, Li Ninghua, Chivese Tawanda, et al. IDF Diabetes Atlas: Global and Regional Estimate of Gestational Diabetes Mellitus Prevalence for 2019-2021 by International Association of Diabetes in Pregnancy Study Group's Criteria [J]. Diabetes research and clinical practice, 2021: 109050-109050.

[2] Zhu Hui, Zhao Zhijia, Xu Jin, et al. The prevalence of gestational diabetes mellitus before and after the implementation of the universal two-child policy in China [J]. Frontiers in Endocrinology, 2022, 13:960877-960877.

[3] Sweeting Arianne, Wong Jencia, Murphy Helen R, et al. A clinical update on Gestational Diabetes Mellitus [J]. Endocrine reviews, 2022, 43(5):763-793.

[4] Zhang TN, Huang XM, Zhao XY, Wang W, Wen R, Gao SY. Risks of specific congenital anomalies in offspring of women with diabetes: A systematic review and meta-analysis of population-based studies including over 80 million births. PLoS Med. 2022;19(2):e1003900.

[5] Ponnusamy Saravanan, Laura A Magee, Anita Banerjee, et al. Gestational diabetes: opportunities for improving maternal and child health [J]. The Lancet Diabetes & Endocrinology, 2020, 8(9):793-800.

[6] Eizirik Décio L, Pasquali Lorenzo, Cnop Miriam, et al. Pancreatic β-cells in type 1 and type 2 diabetes mellitus: different pathways to failure [J]. Nature reviews. Endocrinology, 2020, 16(7):349-362.

[7] Frances M. Ashcroft, Patrik Rorsman. Diabetes Mellitus and the β Cell: The Last Ten Years [J]. Cell, 2012, 148(6):1160-1171.

[8] Maria Lytrivi, Anne-Laure Castell, Vincent Poitout, et al. Recent Insights Into Mechanisms of β-Cell Lipo- and Glucolipotoxicity in Type 2 Diabetes [J]. Journal of Molecular Biology, 2020, 432(5):1514-1534.

[9] Jacovetti Cécile, Regazzi Romano. Mechanisms Underlying the Expansion and Functional Maturation of β-Cells in Newborns: Impact of the Nutritional Environment [J]. International Journal of Molecular Sciences, 2022, 23(4):2096-2096.

[10] Kahraman Sevim, Dirice Ercument, De Jesus Dario F, et al. Maternal insulin resistance and transient hyperglycemia impact the metabolic and endocrine phenotypes of offspring [J]. American journal of physiology. Endocrinology and metabolism, 2014, 307(10): E906-918.

[11] Sarah M. Comstock, Lynley D. Pound, Jacalyn M. Bishop, et al. High-fat diet consumption during pregnancy and the early post-natal period leads to decreased α cell plasticity in the nonhuman primate [J]. Molecular Metabolism, 2013, 2(1):10-22.

[12] Carroll Darian T, Elsakr Joseph M, Miller Allie, et al. Maternal Western-style diet in non-human primates leads to offspring islet adaptations including altered gene expression and insulin hypersecretion [J]. American journal of physiology. Endocrinology and metabolism, 2023, 324(6):E577-E588.

[13] Joseph M. Elsakr, Jennifer C. Dunn, Katherine Tennant, et al. Maternal Western-style diet affects offspring islet composition and function in a non-human primate model of maternal over-nutrition [J]. Molecular Metabolism, 2019, 25:73-82.

[14] Agarwal Prasoon, Brar Navdeep, Morriseau Taylor S, et al. Gestational Diabetes Adversely Affects Pancreatic Islet Architecture and Function in the Male Rat Offspring [J]. Endocrinology, 2019, 160(8):1907-1925.

[15] Han Junying, Xu Jianxiang, Long Yunshi, et al. Rat maternal diabetes impairs pancreatic beta-cell function in the

*offspring [J]. American journal of physiology. Endocrinology and metabolism, 2007, 293(1):E228-236.*

[16] Aerts L, Sodoyez-Goffaux F, Sodoyez J C, et al. *The diabetic intrauterine milieu has a long-lasting effect on insulin secretion by B cells and on insulin uptake by target tissues [J]. American journal of obstetrics and gynecology, 1988, 159(5):1287-1292.*

[17] Kelstrup Louise, Damm Peter, Mathiesen Elisabeth R, et al. *Insulin resistance and impaired pancreatic β-cell function in adult offspring of women with diabetes in pregnancy [J]. The Journal of clinical endocrinology and metabolism, 2013, 98(9):3793-3801.*

[18] Scholtens Denise M, Kuang Alan, Lowe Lynn P, et al. *Hyperglycemia and Adverse Pregnancy Outcome Follow-up Study (HAPO FUS): Maternal Glycemia and Childhood Glucose Metabolism [J]. Diabetes care, 2019, 42(3):381-392.*

[19] Nyman Lara R, Wells K Sam, Head W Steve, et al. *Real-time, multidimensional in vivo imaging used to investigate blood flow in mouse pancreatic islets [J]. The Journal of clinical investigation, 2008, 118(11):3790-3797.*

[20] Pound Lynley D, Comstock Sarah M, Grove Kevin L, et al. *Consumption of a Western-style diet during pregnancy impairs offspring islet vascularization in a Japanese macaque model [J]. American journal of physiology. Endocrinology and metabolism, 2014, 307(1):E115-123.*

[21] Gao Jinlong, Huang Tao, Li Jiaomei, et al. *Beneficial Effects of n-3 Polyunsaturated Fatty Acids on Offspring's Pancreas of Gestational Diabetes Rats [J]. Journal of agricultural and food chemistry, 2019, 67(48):13269-13281.*

[22] Marchetti P, Bugliani M, Lupi R, et al. *The endoplasmic reticulum in pancreatic beta cells of type 2 diabetes patients [J]. Diabetologia, 2007, 50(12):2486-2494.*

[23] Laybutt D R, Preston A M, Akerfeldt M C, et al. *Endoplasmic reticulum stress contributes to beta cell apoptosis in type 2 diabetes [J]. Diabetologia, 2007, 50(4):752-763.*

[24] Soeda Jumpei, Mouralidarane Angelina, Cordero Paul, et al. *Maternal obesity alters endoplasmic reticulum homeostasis in offspring pancreas [J]. Journal of physiology and biochemistry, 2016, 72(2):281-291.*

[25] Kawahito Shinji, Kitahata Hiroshi, Oshita Shuzo, et al. *Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress [J]. World journal of gastroenterology, 2009, 15(33):4137-4142.*

[26] Eriksson U J, Borg L A. *Protection by free oxygen radical scavenging enzymes against glucose-induced embryonic malformations in vitro [J]. Diabetologia, 1991, 34(5):325-331.*

[27] Eriksson U J, Borg L A. *Diabetes and embryonic malformations. Role of substrate-induced free-oxygen radical production for dysmorphogenesis in cultured rat embryos [J]. Diabetes, 1993, 42(3):411-419.*

[28] Nicholas Lisa M, Nagao Mototsugu, Kusinski Laura C, et al. *Exposure to maternal obesity programs sex differences in pancreatic islets of the offspring in mice [J]. Diabetologia, 2020, 63(2):324-337.*

[29] Zhu Hong, Chen Bin, Cheng Yi, et al. *Insulin Therapy for Gestational Diabetes Mellitus Does Not Fully Protect Offspring From Diet-Induced Metabolic Disorders [J]. Diabetes, 2019, 68(4):696-708.*

[30] Asahara Shunichiro, Matsuda Tomokazu, Kido Yoshiaki, et al. *Increased ribosomal biogenesis induces pancreatic beta cell failure in mice model of type 2 diabetes [J]. Biochemical and biophysical research communications, 2009, 381(3):367-371.*

[31] Maedler Kathrin, Sergeev Pavel, Ris Frédéric, et al. *Glucose-induced beta cell production of IL-1beta contributes to glucotoxicity in human pancreatic islets [J]. The Journal of clinical investigation, 2002, 110(6):851-860.*

[32] Ding Guolian, Wang Fangfang, Shu Jing, et al. *Transgenerational glucose intolerance with Igf2/H19 epigenetic alterations in mouse islet induced by intrauterine hyperglycemia [J]. Diabetes, 2012, 61(5):1133-1142.*

[33] Estil les Elisabet, Téllez Nòdia, Soler Joan, et al. *High sensitivity of beta-cell replication to the inhibitory effects of interleukin-1beta: modulation by adenoviral overexpression of IGF2 in rat islets [J]. The Journal of endocrinology, 2009, 203(1):55-63.*

[34] Zahra Nazari, Mohammad Nabiuni, Mohsen Saeidi, et al. *Gestational diabetes leads to down-regulation of CDK4-pRB-E2F1 pathway genes in pancreatic islets of rat offspring [J]. Iranian Journal of Basic Medical Sciences, 2017, 20(2):150-154.*

[35] Nazari Zahra, Shahryari Alireza, Ghafari Soraya, et al. *In Utero Exposure to Gestational Diabetes Alters DNA Methylation and Gene Expression of CDKN2A/B in Langerhans Islets of Rat Offspring [J]. Cell journal, 2020, 22(2):203-211.*

[36] Henriikka Salomäki, Merja Heinäniemi, Laura H Vähätalo, et al. *Prenatal metformin exposure in a maternal high fat diet mouse model alters the transcriptome and modifies the metabolic responses of the offspring [J]. PLoS ONE, 2017, 9(12):e115778.*

[37] Carlson Zach, Hafner Hannah, Mulcahy Molly, et al. *Lactational metformin exposure programs offspring white adipose tissue glucose homeostasis and resilience to metabolic stress in a sex-dependent manner [J]. American journal of physiology. Endocrinology and metabolism, 2020, 318(5):E600-E612.*

[38] Nguyen Linh, Lim Lillian Yuxian, Ding Shirley Suet Lee, et al. *Metformin perturbs pancreatic differentiation from human embryonic stem cells [J]. Diabetes, 2021, 70(8): p. 1689-1702.*