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Minireview

Maternal Diabetes Mellitus and the Origin of Non-Communicable Diseases in Offspring: The Role of Epigenetics[1]

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ABSTRACT

Offspring of diabetic mothers are susceptible to the onset of metabolic syndromes, such as type 2 diabetes and obesity at adulthood, and this trend can be inherited between generations. Genetics cannot fully explain how the noncommunicable disease in offspring of diabetic mothers is caused and inherited by the next generations. Many studies have confirmed that epigenetics may be crucial for the detrimental effects on offspring exposed to the hyperglycemic environment. Although the adverse effects on epigenetics in offspring of diabetic mothers may be the result of the poor intrauterine environment, epigenetic modifications in oocytes of diabetic mothers are also affected. Therefore, the present review is focused on the epigenetic alterations in oocytes and embryos of diabetic mothers. Furthermore, we also discuss initial mechanistic insight on maternal diabetes mellitus causing alterations of epigenetic modifications.

embryo, epigenetics, maternal diabetes, offspring, oocyte

INTRODUCTION

Diabetes mellitus is a chronic disease characterized by elevated blood glucose levels, impaired insulin secretion, and/or peripheral resistance to insulin action. As of 2012, more than 371 million people were reported to have diabetes mellitus, and most of them were distributed throughout the developing countries, such as China and India [1]. Not only does diabetes mellitus cause many complications for patients, but their offspring have a higher risk of malformations [2]. Furthermore, maternal diabetes mellitus can affect the offspring's health by increasing the risk for some noncommunicable disorders in adulthood [3–5]. A large number of epidemiologic studies revealed that infants of diabetic mothers are more susceptible to complex diseases, such as obesity [6], type 2 diabetes [7], cardiovascular complications [8], and even cancer [9]. Although preexisting insulin-dependent diabetes mellitus in women can be well controlled, these women still experience a three- to fivefold higher incidence of pregnancy complications [10, 11]. The risk for non-communicable diseases may be caused by epigenetic variations because genetics explains only a small proportion of the effects [12, 13]. The ''Barker hypothesis,'' stating that undernutrition before birth induces persisting changes in a range of metabolic, physiological, and structural parameters, may explain this phenomenon very well [13].

Furthermore, maternal diabetes mellitus injures ovarian function and oogenesis [14]; developmental anomalies induced by maternal diabetes mellitus are also found in the embryo and fetus [15, 16]. These data indicate that the early environmental exposure to maternal diabetes may be a key reason for the offspring's impaired health in adulthood. Epigenetics provides a link between genes and the environment, and epigenetic alterations can be inherited by the next generation. Therefore, this review is focused on the epigenetic changes in oocytes and embryos of diabetic mothers and on discussing the relationship between maternal hyperglycemia and epigenetic changes in oocytes and embryos.

EPIGENETICS AND OFFSPRING OF DIABETIC MOTHERS

Early in the 1990s, Dörner and Plagemann showed that exposure to a hyperglycemic intrauterine environment increases the risk of obesity and diabetes in offspring [17]; similar conclusions were reported in a large number of epidemiological studies, indicating that children exposed to a diabetic intrauterine environment have an increased risk of developing obesity, type 2 diabetes mellitus, and metabolic syndrome, among other chronic diseases, later in life [9, 18–21]. However, the mechanism(s) underlying the increased risk of obesity and diabetes in offspring of diabetic mothers are not well understood.

Epigenetics and Candidate Genes

Epigenetic modifications are generally assumed to mediate gene-environment interactions, leading to persistent changes of gene regulation and metabolic pathways [22, 23]. Studies indicate that changes in DNA methylation of specific sequences, one of the most stable and best understood

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TABLE 1. Spectrum of epigenetic alterations in oocytes, embryos, and offspring of diabetic mothers.

Tissue(s)	Epigenetic alteration(s)	Species	Reference(s)
Oocyte	Histone acetylation	Mouse	[68]
Oocyte	DNA methylation of imprinted genes	Mouse	[64]
Oocyte	Expression of epigenetic-associated genes	Mouse	[72]
Neurulation stage embryo	Genome-wide acetylation of histone	Mouse	[44]
Fetus	DNA methylation of H19 and Igf2	Mouse	[42]
Embryo	DNA methylation of imprinted genes	Mouse	[43]
Cord blood and placenta tissue	DNA methylation of imprinted genes and some nonimprinted genes	Human	[32]
Placenta	DNA methylation of adiponectin gene and leptin	Human	[28, 31]
Cord blood and placenta tissue	DNA methylation of ATP-binding cassette transporter A1	Human	[33]
Cord blood and placenta tissue	Genome-wide DNA methylation analysis	Human	[36]
Cord blood and placenta tissue	Global methylation	Human	[35]
Cord blood and placenta tissue	DNA methylation of MEST	Human	[32]
Blood of children	Global analysis of DNA methylation	Human	[37]
Islet and sperm of offspring (F1 and F2)	DNA methylation of H19 and Igf2	Mouse	[30]

epigenetic modifications [24], may result in obesity and diabetes mellitus [25, 26] (Table 1). When glucose tolerance is impaired during gestation, DNA methylation levels in the leptin gene promoter are altered in placentas, resulting in a reduction of its expression [27]. Mice derived from streptozotocin (STZ)-induced diabetic dams showed impairments in metabolic regulation that were associated with leptin resistance during adulthood. Furthermore, the ability of leptin to activate intracellular signaling in arcuate neurons was also significantly reduced in neonates born to diabetic dams [28]. Recently, Ding et al. [29] found that the methylation status of the differentially methylated regions of *H19* and *Igf2* was altered in islets of F1 and F2 offspring from gestational diabetes mellitus and that their expressions were also down-regulated in the STZ-induced mice model.

Another study showed that DNA methylation in the promoter of the adiponectin gene on the fetal side of the placenta is inversely correlated with maternal glucose levels during the second trimester of pregnancy [30]. El Hajj et al. [31] analyzed the DNA methylation patterns of several genes in placental tissues and cord blood from 88 newborns of mothers with dietetically treated gestational diabetes mellitus, 98 with insulin-dependent gestational diabetes mellitus, and 65 without gestational diabetes mellitus. The results showed that the methylation level of the maternally imprinted MEST gene, nonimprinted glucocorticoid receptor NR3C1, and interspersed ALU repeats was decreased in gestational diabetes mellitus in both analyzed samples when compared with controls. The different blood MEST methylation was also observed in morbid obese adults compared with normal-weight controls. Further studies showed that the DNA methylation levels of ATP-binding cassette transporter A1 in cord blood and placental tissues were associated with glucose and cord blood triglyceride levels [32]. These independent studies all indicate that epigenetic changes could contribute to explaining the detrimental health effects associated with fetal programming, such as increased risk of obesity and type 2 diabetes mellitus in offspring of diabetic mothers.

Epigenetics and Genome-Wide Methylation

To investigate the whole DNA methylation status of tissues from offspring exposed to maternal diabetes, Li et al. [33] utilized a mouse model to evaluate the cytosine methylation levels in livers from offspring of obese and diabetic mothers. The results showed that although gene expression was widely affected, there were subtle alterations in cytosine methylation. However, Nomura et al. [34] showed in patients with gestational diabetes that the global methylation levels in the placenta were lower compared with patients without gestational diabetes. They suggest that the abnormal global methylation level in the placenta is associated with an abnormal infant body length and head circumference. Similar results in offspring from diabetic mothers were reported in another study; the methylation status at more than 485 000 CpG sites was analyzed in the placenta and umbilical blood of offspring exposed to gestational diabetes mellitus. The results indicated that 3271 and 3758 genes in the placenta and cord blood, respectively, were potentially differentially methylated between samples either exposed or not exposed to gestational diabetes mellitus and that more than 25% of the genes were common to both samples. Eleven percent of the genes were likely involved in the metabolic disease pathways [35]. To identify the candidate genes and biological pathways associated with differentially methylated regions in relation to exposure to gestational diabetes mellitus, West et al. [36] investigated the DNA methylation patterns at more than 27 000 CpG sites of peripheral blood from offspring, ranging from 8 to 12 yr of age, either exposed or not exposed to the diabetic environment during pregnancy. They identified some variations in genome-wide DNA methylation patterns resulting from intrauterine exposure to maternal gestational diabetes mellitus, and many of them were linked to metabolic diseases in the offspring of diabetic mothers. These studies indicate that epigenetic changes may play a key role in the detrimental effects on offspring of diabetic mothers.

EPIGENETICS AND EMBRYOS OF DIABETIC FEMALES

While previous studies indicated that epigenetic modifications in offspring of diabetic mothers occur, the detailed underlying mechanisms are still unclear. As epigenetics can be affected during the neonatal period, the Barker hypothesis established that the adverse intrauterine environment may be an important factor for the risk of diseases in offspring [13]. In humans and animal models, if nutrient intake is imbalanced during pregnancy, fetal growth is restricted, increasing the exposed offspring's susceptibility to insulin resistance, diabetes, and obesity later in life [37–39]. These disease risks in offspring may be associated with epigenetic changes. In the nutrient-restricted model, epigenetic modifications including DNA methylation and histone modification are changed in many tissues of the fetus [40]. The epigenetic modifications in offspring of diabetic mothers are also altered (Table 1). In the streptozotocin-induced mouse model, the mRNA expression of *Igf2* and the methylation level of the H19-Igf2 imprint control region were changed in fetuses on Embryonic Day 14

compared with control dams [41]. In our laboratory, we investigated the DNA methylation patterns in differentially methylated regions of imprinted *Peg3*, *Snrpn*, and *H19* in fetuses and placental tissues on Day Postcoitum (dpc) 10.5 utilizing the streptozotocin-induced mouse model [42]. We found that the methylation status of *Peg3*, *Snrpn*, and *H19* in dpc-10.5 fetuses was not altered by the diabetic intrauterine environment but that the methylation patterns of *Peg3* and *H19* were changed in the dpc-10.5 placentas. The changes of mRNA expression of *Peg3* in dpc-10.5 placentas in the groups coincided with the DNA methylation patterns.

The histone modifications in the offspring from diabetic females have also been found to be altered. Salbaum and Kappen [43] observed that maternal diabetes and exposure to a high-fat diet caused alterations in H3 and H4 histone acetylation in the embryos. Changes of H3K27 acetylation marks were significantly enriched near genes known to cause neural tube defects in mouse E8.5 embryos from diabetic mothers. These results for embryos from diabetic pregnancies support the notion that maternal diabetic distress, as brought about by hyperglycemia, alters patterns of histone modification across the genome [44].

Although these data provide molecular evidence to support the changes of epigenetics evoked by the adverse intrauterine environment, how the diabetic intrauterine environment causes epigenetic alterations remains unanswered. Jimenez-Chillaron et al. [45] and Stoffers et al. [46] indicate that there are critical periods of developmental plasticity during which nutritional and pharmacological interventions can reverse abnormal metabolic functions and reduce the risk of adulthood disease. Smith et al. [47] suggest that preimplantation development is a unique developmental period where methylation is differentially positioned and regulated before being restored and maintained in a somatic fashion. This indicates that this period is a key window for establishing the somatic DNA methylation patterns. However, studies have confirmed that the metabolism of early embryos is affected by maternal hyperglycemia. In the in vivo mouse model, maternal hyperglycemia down-regulated the embryonic facilitative glucose transporters 1, 2, and 3 at the blastocyst stage of development [48]; in vitro studies in which two-cell embryos were cultured for 72 h in high concentrations of glucose (30 or 52 mM) also resulted in decreased mRNA and protein expressions of the facilitative transporters [48–50]. Therefore, the utilization of glucose was also affected in early embryos of diabetic mothers. Glucose availability can affect histone acetylation in an adenosine triphosphate-citrate lysase (ACL)-dependent manner [51]. ACL is required for increases in histone acetylation in response to growth factor stimulation and during differentiation, and histone acetylation can be affected by glucose availability. These data indicate that abnormal glucose metabolism may play a key role in the alterations of epigenetics in embryos.

EPIGENETICS AND OOCYTES OF DIABETIC MOTHERS

The intrauterine environment has an important effect on embryonic development and the offspring's health [16, 52]; however, when the one-cell-stage embryo of diabetic mothers is transferred to nondiabetic pseudopregnant recipients, the malformation of embryos is still observed in the streptozotocin-induced mouse model [53]. This finding suggests that embryo development is not the only susceptible period for the onset of metabolic diseases in the offspring from diabetic mothers. During oogenesis, the DNA methylation is erased and is then almost completely reestablished at the metaphase II stage [54]. The DNA methylation status of CpG islands in oocytes is a critical factor in determining methylation patterns in preimplantation embryos [55]. During oogenesis, the DNA methylation patterns are susceptible to being altered in oocytes. For example, the DNA methylation patterns are abnormal in oocytes of old mice [56]; if the methyl donor levels are lower in the culture medium during mouse follicle culture, the DNA methylation status of oocytes is altered [57]. Postovulatory oocyte aging also induces abnormal DNA methylation in oocytes [58].

Oocyte quality of diabetic females is compromised by the hyperglycemic environment. Communication between oocytes and cumulus cells is reduced due to the decreased expression of gap junction and connexin proteins [59]. The abnormal expression of the glucose transporters impairs glucose metabolism in oocytes, altering their metabolism [49, 60]. Glucose and pyruvate are crucial for nuclear and cytoplasmic maturation of oocytes [61, 62]. Establishing proper DNA methylation is an important event during nuclear maturation of oocytes, and the DNA remethylation process in oocytes is sensitive to the environment. Recently, we showed that female mice fed with high-fat diet after weaning had altered DNA methylation patterns of *Leptin* and *Ppar-*α in oocytes at 15 wk of age [63]. We also investigated the effects of maternal diabetes mellitus on DNA methylation patterns of imprinted genes in oocytes using a streptozotocin-induced diabetic mouse model and nonobese diabetic mouse model (NOD) [64]. In the following, we will give a brief summary of our findings.

By combined bisulfite restriction analysis (COBRA) and bisulfite sequencing (BS) [64], we found that the DNA methylation patterns of *Peg3* and *Snrpn* were not altered in MII oocytes of diabetic females on Day 15 and 25 after injection of streptozotocin. But on Day 35, the methylation status of *Peg3* was significantly decreased in oocytes of diabetic females compared with oocytes of nondiabetic females. Similar results were obtained in NOD mice. This indicates that the DNA methylation pattern of *Peg3* was altered by maternal diabetes mellitus in a time-dependent manner in these mouse models. We also evaluated the expression of DNA methyltransferases (DNMTs) in oocytes by real-time PCR. We found that the expression of DNMT1, DNMT3a, DNMT3b, and DNMT3l in oocytes of diabetic females, compared with the expression in oocytes of nondiabetic females, was also decreased in a time-dependent manner. DNA methylation reestablishment in oocytes is catalyzed mainly by DNMT3a and DNMT3b, which are coordinately regulated [65, 66]. In our study, we found that the decreased expression of DNMTs may cause the alterations of DNA methylation of *Peg3*. Ding et al. [67] reported that the histone acetylation in oocytes of mice was also changed by maternal diabetes.

At 15 days after injection of streptozotocin, we mated the female diabetic mice and/or nondiabetic mice with nondiabetic male mice and then evaluated the DNA methylation level of the imprinted genes in oocytes from offspring of diabetic and nondiabetic mothers by COBRA and BS. We found that the DNA methylation status of the analyzed imprinted genes was not changed. This coincided with the methylation patterns of oocytes from diabetic females. However, the genome-wide DNA methylation patterns in oocytes from offspring of diabetic mothers were still unclear because we analyzed only the DNA methylation patterns of *H19*, *Peg3*, and *Snrpn* in oocytes of offspring from diabetic mothers. It is also still unclear whether the DNA methylation patterns and histone modifications of other genes in oocytes are altered by maternal diabetes mellitus and whether the deleterious effects of maternal diabetes mellitus on offspring is transmitted to the next generations by germ cells.

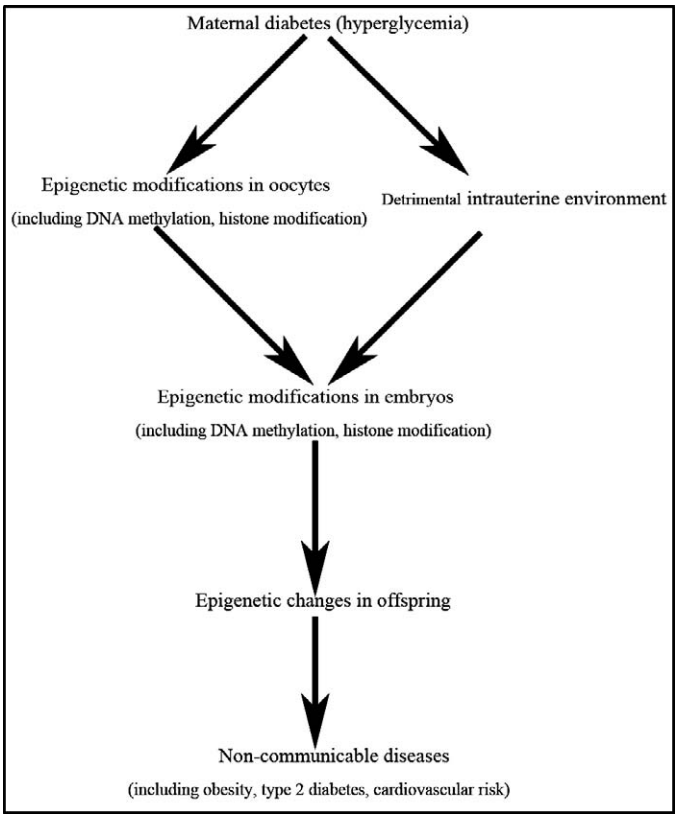

FIG. 1. The potential role of hyperglycemia in causing the epigenetic alterations in offspring of diabetic mothers. The maternal hyperglycemia may induce the changes in epigenetics and gene expressions in oocytes and evoked by the adverse intrauterine environment. The epigenetic modifications in embryos may be affected by the changed epigenetic modifications and gene expressions in oocytes and the detrimental intrauterine environment. These changes in epigenetic modification can be maintained through adulthood and contribute to the metabolic disorders.

Overall, we revealed that the DNA methylation patterns of imprinted genes in oocytes were altered by maternal diabetes mellitus [64]. These data indicate that metabolic diseases in offspring from diabetic mothers may be initiated in oocytes (Table 1).

UNDERLYING MECHANISMS: HYPERGLYCEMIA AND EPIGENETICS

As discussed above, the epigenetic modification of offspring may be altered by maternal diabetes mellitus, which may be a crucial reason for metabolic diseases in offspring from disease-affected mothers. Not only does the intrauterine hyperglycemic environment play a significant role in the alterations of epigenetic modifications in the development of disease [68], but the hyperglycemic environment of maternal diabetes also has deleterious effects on the proper epigenetic establishment of oocytes [64]. Glucose is crucial for nuclear and cytoplasmic maturation of oocytes [61, 62] (Fig. 1). Maternal hyperglycemia decreases de novo purine and cAMP synthesis and induces poor nuclear maturation of oocytes because the flux of glucose through the pentose phosphate pathway is decreased [69]. Although the flux of glucose through glycolysis was not affected [69], the AMP:ATP ratio was increased in denuded oocytes from diabetic mice [70]. This indicates that intracellular ATP is rapidly used [70]. Wellen et al. [51] reported that ATP-citrate lysase was crucial for histone modification. Ding et al. [67] reported that the histone acetylation in oocytes of mice was changed by maternal diabetes. This indicates that the maternal hyperglycemia may be a crucial reason for the alteration of epigenetic modifications of oocytes. The mRNA expression profile of oocytes from diabetic mice was significantly affected compared to controls [71]. Many of the affected genes are included in the metabolism and epigenetic modifications [71], so these may directly contribute to the abnormal establishment of epigenetics in oocytes from diabetic mice.

In cleavage-stage embryos, glucose is not the main fuel for many species until compaction and blastocyst formation. However, as in oocytes, glucose is crucial for DNA modification in early embryos [43, 44]. The changed expression of glucose transporters, such as GLUT1, 2, 3 [48] and MCT (H^+-monocarboxylate cotransporter) [72], in early embryos exposed to a hyperglycemic condition may crucially contribute to the changed epigenetic modifications. The changed expression of epigenetic-associated genes in oocytes of diabetic mothers may be another reason for the changed histone modification of embryos exposed to the hyperglycemic environment [43] because the reserved proteins in oocytes are vital for early embryonic development [73] (Fig. 1).

CONCLUSIONS AND PERSPECTIVES

From the above discussion, we conclude that the epigenetic alterations in offspring from maternal mothers may originate, in addition to the intrauterine environment, from oocytes and that the maternal hyperglycemic environment may be a main reason for the detrimental effects on epigenetics in oocytes and embryos. However, the detailed mechanism(s) causing the alteration of epigenetics are still not completely understood.

Although the DNA methylation and histone modification in oocytes and embryos are negatively affected by maternal diabetes mellitus, how maternal diabetes mellitus induces this detrimental effect on epigenetics is still incompletely understood. Hyperglycemia may not be the only factor because the risk of metabolic syndrome in adult offspring of women with controlled gestational diabetes mellitus or type 1 diabetes compared with adult offspring from the background population is increased 4- and 2.5-fold, respectively [7]. Therefore, discovering whether there are other factors included in causing epigenetic alterations in offspring of diabetic mothers is needed. The detailed underlying mechanism of how glucose causes the epigenetic changes is also poorly understood.

Offspring of severely and mildly hyperglycemic mothers (the second generation) developed gestational diabetes, and their offspring, the third generation, also displayed a similar metabolic syndrome as offspring of mildly hyperglycemic mothers [74, 75]. This indicates that the effects on offspring exposed to maternal diabetes can be transmitted to the next generations, but genetics alone cannot completely explain this phenomenon because the effect is induced by the interaction between genes and the environment. Epigenetic modifications are generally assumed to mediate gene-environment interactions, leading to persistent changes of gene regulation and metabolic pathways [22, 23]. However, how the alterations of epigenetics in offspring of maternal diabetes are transmitted to the next generations by oocytes is poorly understood. In humans, although the number of diabetic individuals is increasing rapidly, it is difficult to look for the mechanism(s) underlying the inheritance of detrimental effects on offspring exposed to maternal diabetes between generations. Therefore, we need to use appropriate animal models to investigate how

maternal diabetes transmits the changed epigenetic modifications to the next generations.

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REFERENCES

1. International Diabetes Federation [Internet]. Brussels, Belgium: International Diabetes Federation. http://www.idf.org/worlddiabetesday/toolkit/gp/facts-figures. Accessed 5 December 2013.
2. Zabihi S, Loeken MR. Understanding diabetic teratogenesis: where are we now and where are we going? Birth Defects Res A Clin Mol Teratol 2010; 88:779–790.
3. Yajnik CS. Nutrient-mediated teratogenesis and fuel-mediated teratogenesis: two pathways of intrauterine programming of diabetes. Int J Gynaecol Obstet 2009; 104(suppl 1):S27–S31.
4. Schwartz R. Hyperinsulinemia and macrosomia. N Engl J Med 1990; 323: 340–342.
5. Hawdon JM. Babies born after diabetes in pregnancy: what are the short- and long-term risks and how can we minimise them? Best Pract Res Clin Obstet Gynaecol 2011; 25:91–104.
6. Desai M, Beall M, Ross MG. Developmental origins of obesity: programmed adipogenesis. Curr Diab Rep 2013; 13:27–33.
7. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, Schmidt L, Damm P. Overweight and the metabolic syndrome in adult offspring of women with diet-treated gestational diabetes mellitus or type 1 diabetes. J Clin Endocrinol Metab 2009; 94: 2464–2470.
8. Wright CS, Rifas-Shiman SL, Rich-Edwards JW, Taveras EM, Gillman MW, Oken E. Intrauterine exposure to gestational diabetes, child adiposity, and blood pressure. Am J Hypertens 2009; 22:215–220.
9. Wu CS, Nohr EA, Bech BH, Vestergaard M, Olsen J. Long-term health outcomes in children born to mothers with diabetes: a population-based cohort study. PLoS One 2012; 7:e36727.
10. Casson IF, Clarke CA, Howard CV, McKendrick O, Pennycook S, Pharoah PO, Platt MJ, Stanisstreet M, van Velszen D, Walkinshaw S. Outcomes of pregnancy in insulin dependent diabetic women: results of a five year population cohort study. BMJ 1997; 315:275–278.
11. Greene MF. Spontaneous abortions and major malformations in women with diabetes mellitus. Semin Reprod Endocrinol 1999; 17:127–136.
12. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, Cho JH, Guttmacher AE, et al. Finding the missing heritability of complex diseases. Nature 2009; 461:747–753.
13. Barker DJ. Fetal origins of coronary heart disease. BMJ 1995; 311: 171–174.
14. Tatone C, Heizenrieder T, Di Emidio G, Treffon P, Amicarelli F, Seidel T, Eichenlaub-Ritter U. Evidence that carbonyl stress by methylglyoxal exposure induces DNA damage and spindle aberrations, affects mitochondrial integrity in mammalian oocytes and contributes to oocyte ageing. Hum Reprod 2011; 26:1843–1859.
15. Amaral S, Oliveira PJ, Ramalho-Santos J. Diabetes and the impairment of reproductive function: possible role of mitochondria and reactive oxygen species. Curr Diabetes Rev 2008; 4:46–54.
16. Jungheim ES, Moley KH. The impact of type 1 and type 2 diabetes mellitus on the oocyte and the preimplantation embryo. Semin Reprod Med 2008; 26:186–195.
17. Dorner G, Plagemann A. Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life. Horm Metab Res 1994; 26:213–221.
18. Lawlor DA, Lichtenstein P, Langstrom N. Association of maternal diabetes mellitus in pregnancy with offspring adiposity into early adulthood: sibling study in a prospective cohort of 280,866 men from 248,293 families. Circulation 2011; 123:258–265.
19. Crume TL, Ogden L, Daniels S, Hamman RF, Norris JM, Dabelea D. The impact of in utero exposure to diabetes on childhood body mass index growth trajectories: the EPOCH study. J Pediatr 2011; 158:941–946.
20. Dabelea D, Mayer-Davis EJ, Lamichhane AP, D'Agostino RB Jr., Liese AD, Vehik KS, Narayan KM, Zeitler P, Hamman RF. Association of intrauterine exposure to maternal diabetes and obesity with type 2 diabetes in youth: the SEARCH Case-Control Study. Diabetes Care 2008; 31: 1422–1426.
21. Dabelea D, Pettitt DJ. Intrauterine diabetic environment confers risks for type 2 diabetes mellitus and obesity in the offspring, in addition to genetic susceptibility. J Pediatr Endocrinol Metab 2001; 14:1085–1091.
22. Fernandez-Gonzalez R, Moreira P, Bilbao A, Jimenez A, Perez-Crespo M, Ramirez MA, Rodriguez De Fonseca F, Pintado B, Gutierrez-Adan A. Long-term effect of in vitro culture of mouse embryos with serum on mRNA expression of imprinting genes, development, and behavior. Proc Natl Acad Sci U S A 2004; 101:5880–5885.
23. Hanson MA, Low FM, Gluckman PD. Epigenetic epidemiology: the rebirth of soft inheritance. Ann Nutr Metab 2011; 58(suppl 2):8–15.
24. Bird A. DNA methylation patterns and epigenetic memory. Genes Dev 2002; 16:6–21.
25. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, Susser ES, Slagboom PE, Lumey LH. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc Natl Acad Sci U S A 2008; 105:17046–17049.
26. Stoger R. The thrifty epigenotype: an acquired and heritable predisposition for obesity and diabetes? Bioessays 2008; 30:156–166.
27. Bouchard L, Thibault S, Guay SP, Santure M, Monpetit A, St-Pierre J, Perron P, Brisson D. Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy. Diabetes Care 2010; 33: 2436–2441.
28. Steculorum SM, Bouret SG. Maternal diabetes compromises the organization of hypothalamic feeding circuits and impairs leptin sensitivity in offspring. Endocrinology 2011; 152:4171–4179.
29. Ding GL, Wang FF, Shu J, Tian S, Jiang Y, Zhang D, Wang N, Luo Q, Zhang Y, Jin F, Leung PC, Sheng JZ, et al. Transgenerational glucose intolerance with Igf2/H19 epigenetic alterations in mouse islet induced by intrauterine hyperglycemia. Diabetes 2012; 61:1133–1142.
30. Bouchard L, Hivert MF, Guay SP, St-Pierre J, Perron P, Brisson D. Placental adiponectin gene DNA methylation levels are associated with mothers' blood glucose concentration. Diabetes 2012; 61:1272–1280.
31. El Hajj N, Pliushch G, Schneider E, Dittrich M, Muller T, Korenkov M, Aretz M, Zechner U, Lehnen H, Haaf T. Metabolic programming of MEST DNA methylation by intrauterine exposure to gestational diabetes mellitus. Diabetes 2013; 62:1320–1328.
32. Houde AA, Guay SP, Desgagne V, Hivert MF, Baillargeon JP, St-Pierre J, Perron P, Gaudet D, Brisson D, Bouchard L. Adaptations of placental and cord blood ABCA1 DNA methylation profile to maternal metabolic status. Epigenetics 2013; 1289–1302.
33. Li CC, Young PE, Maloney CA, Eaton SA, Cowley MJ, Buckland ME, Preiss T, Henstridge DC, Cooney GJ, Febbraio MA, Martin DI, Cropley JE, et al. Maternal obesity and diabetes induces latent metabolic defects and widespread epigenetic changes in isogenic mice. Epigenetics 2013; 8: 602–611.
34. Nomura Y, Lambertini L, Rialdi A, Lee M, Mystal EY, Grabie M, Manaster I, Huynh N, Finik J, Davey M, Davey K, Ly J, et al. Global methylation in the placenta and umbilical cord blood from pregnancies with maternal gestational diabetes, preeclampsia, and obesity. Reprod Sci 2013; 21:131–137.
35. Ruchat SM, Houde AA, Voisin G, St-Pierre J, Perron P, Baillargeon JP, Gaudet D, Hivert MF, Brisson D, Bouchard L. Gestational diabetes mellitus epigenetically affects genes predominantly involved in metabolic diseases. Epigenetics 2013; 8:935–943.
36. West NA, Kechris K, Dabelea D. Exposure to maternal diabetes in utero and DNA methylation patterns in the offspring. Immunometabolism 2013; 1:1–9.
37. Lillycrop KA. Effect of maternal diet on the epigenome: implications for human metabolic disease. Proc Nutr Soc 2011; 70:64–72.
38. Vuguin PM. Animal models for small for gestational age and fetal programming of adult disease. Horm Res 2007; 68:113–123.
39. Seki Y, Williams L, Vuguin PM, Charron MJ. Minireview: epigenetic programming of diabetes and obesity: animal models. Endocrinology 2012; 153:1031–1038.
40. Woo M, Patti ME. Diabetes risk begins in utero. Cell Metab 2008; 8:5–7.
41. Shao WJ, Tao LY, Gao C, Xie JY, Zhao RQ. Alterations in methylation and expression levels of imprinted genes H19 and Igf2 in the fetuses of diabetic mice. Comp Med 2008; 58:341–346.
42. Ge ZJ, Liang QX, Luo SM, Wei YC, Han ZM, Schatten H, Sun QY, Zhang CL. Diabetic uterus environment may play a key role in alterations of DNA methylation of several imprinted genes at mid-gestation in mice. Reprod Biol Endocrinol 2013; 11:119.
43. Salbaum JM, Kappen C. Responses of the embryonic epigenome to maternal diabetes. Birth Defects Res A Clin Mol Teratol 2012; 94: 770–781.
44. Salbaum JM, Kappen C. Diabetic embryopathy: a role for the epigenome? Birth Defects Res A Clin Mol Teratol 2011; 91:770–780.
45. Jimenez-Chillaron JC, Hernandez-Valencia M, Lightner A, Faucette RR,

Reamer C, Przybyla R, Ruest S, Barry K, Otis JP, Patti ME. Reductions in caloric intake and early postnatal growth prevent glucose intolerance and obesity associated with low birthweight. Diabetologia 2006; 49: 1974–1984.
46. Stoffers DA, Desai BM, DeLeon DD, Simmons RA. Neonatal exendin-4 prevents the development of diabetes in the intrauterine growth retarded rat. Diabetes 2003; 52:734–740.
47. Smith ZD, Chan MM, Mikkelsen TS, Gu H, Gnirke A, Regev A, Meissner A. A unique regulatory phase of DNA methylation in the early mammalian embryo. Nature 2012; 484:339–344.
48. Moley KH, Chi MM, Mueckler MM. Maternal hyperglycemia alters glucose transport and utilization in mouse preimplantation embryos. Am J Physiol 1998; 275:E38–E47.
49. Zheng P, Vassena R, Latham KE. Effects of in vitro oocyte maturation and embryo culture on the expression of glucose transporters, glucose metabolism and insulin signaling genes in rhesus monkey oocytes and preimplantation embryos. Mol Hum Reprod 2007; 13:361–371.
50. Bermejo-Alvarez P, Roberts RM, Rosenfeld CS. Effect of glucose concentration during in vitro culture of mouse embryos on development to blastocyst, success of embryo transfer, and litter sex ratio. Mol Reprod Dev 2012; 79:329–336.
51. Wellen KE, Hatzivassiliou G, Sachdeva UM, Bui TV, Cross JR, Thompson CB. ATP-citrate lyase links cellular metabolism to histone acetylation. Science 2009; 324:1076–1080.
52. Cox NJ. Maternal component in NIDDM transmission. How large an effect? Diabetes 1994; 43:166–168.
53. Wyman A, Pinto AB, Sheridan R, Moley KH. One-cell zygote transfer from diabetic to nondiabetic mouse results in congenital malformations and growth retardation in offspring. Endocrinology 2008; 149:466–469.
54. Obata Y, Kono T. Maternal primary imprinting is established at a specific time for each gene throughout oocyte growth. J Biol Chem 2002; 277: 5285–5289.
55. Smallwood SA, Tomizawa S, Krueger F, Ruf N, Carli N, Segonds-Pichon A, Sato S, Hata K, Andrews SR, Kelsey G. Dynamic CpG island methylation landscape in oocytes and preimplantation embryos. Nat Genet 2011; 43:811–814.
56. Yue MX, Fu XW, Zhou GB, Hou YP, Du M, Wang L, Zhu SE. Abnormal DNA methylation in oocytes could be associated with a decrease in reproductive potential in old mice. J Assist Reprod Genet 2012; 29: 643–650.
57. Anckaert E, Romero S, Adriaenssens T, Smitz J. Effects of low methyl donor levels in culture medium during mouse follicle culture on oocyte imprinting establishment. Biol Reprod 2010; 83:377–386.
58. Liang XW, Ge ZJ, Guo L, Luo SM, Han ZM, Schatten H, Sun QY. Effect of postovulatory oocyte aging on DNA methylation imprinting acquisition in offspring oocytes. Fertil Steril 2011; 96:1479–1484.
59. Colton SA, Pieper GM, Downs SM. Altered meiotic regulation in oocytes from diabetic mice. Biol Reprod 2002; 67:220–231.
60. Ratchford AM, Chang AS, Chi MM, Sheridan R, Moley KH. Maternal diabetes adversely affects AMP-activated protein kinase activity and cellular metabolism in murine oocytes. Am J Physiol Endocrinol Metab 2007; 293:E1198–E1206.
61. Sutton-McDowall ML, Gilchrist RB, Thompson JG. The pivotal role of glucose metabolism in determining oocyte developmental competence. Reproduction 2010; 139:685–695.
62. Funahashi H, Koike T, Sakai R. Effect of glucose and pyruvate on nuclear and cytoplasmic maturation of porcine oocytes in a chemically defined medium. Theriogenology 2008; 70:1041–1047.
63. Ge ZJ, Luo SM, Lin F, Liang QX, Huang L, Wei YC, Hou Y, Han ZM, Schatten H, Sun QY.DNA methylation in oocytes and liver of female mice and their offspring: effects of high-fat-diet-induced obesity. Environ Health Perspect 2014; 122:159–164.
64. Ge ZJ, Liang XW, Guo L, Liang QX, Luo SM, Wang YP, Wei YC, Han ZM, Schatten H, Sun QY. Maternal diabetes causes alterations of DNA methylation statuses of some imprinted genes in murine oocytes. Biol Reprod 2013; 88:117.
65. Lenzen S. The mechanisms of alloxan- and streptozotocin-induced diabetes. Diabetologia 2008; 51:216–226.
66. Lees-Murdock DJ, Shovlin TC, Gardiner T, De Felici M, Walsh CP. DNA methyltransferase expression in the mouse germ line during periods of de novo methylation. Dev Dyn 2005; 232:992–1002.
67. Ding L, Pan R, Huang X, Wang JX, Shen YT, Xu L, Zhang Y, Liu Y, He XQ, Yang XJ, Qi ZQ, Wang HL. Changes in histone acetylation during oocyte meiotic maturation in the diabetic mouse. Theriogenology 2012; 78:784–792.
68. Stride A, Shepherd M, Frayling TM, Bulman MP, Ellard S, Hattersley AT. Intrauterine hyperglycemia is associated with an earlier diagnosis of diabetes in HNF-1alpha gene mutation carriers. Diabetes Care 2002; 25: 2287–2291.
69. Colton SA, Humpherson PG, Leese HJ, Downs SM. Physiological changes in oocyte-cumulus cell complexes from diabetic mice that potentially influence meiotic regulation. Biol Reprod 2003; 69:761–770.
70. Ratchford AM, Esguerra CR, Moley KH. Decreased oocyte-granulosa cell gap junction communication and connexin expression in a type 1 diabetic mouse model. Mol Endocrinol 2008; 22:2643–2654.
71. Ma JY, Li M, Ge ZJ, Luo Y, Ou XH, Song S, Tian D, Yang J, Zhang B, Ou-Yang YC, Hou Y, Liu Z, et al. Whole transcriptome analysis of the effects of type I diabetes on mouse oocytes. PLoS One 2012; 7:e41981.
72. Jansen S, Esmaeilpour T, Pantaleon M, Kaye PL. Glucose affects monocarboxylate cotransporter (MCT) 1 expression during mouse preimplantation development. Reproduction 2006; 131:469–479.
73. Antczak M, Van Blerkom J. Oocyte influences on early development: the regulatory proteins leptin and STAT3 are polarized in mouse and human oocytes and differentially distributed within the cells of the preimplantation stage embryo. Mol Hum Reprod 1997; 3:1067–1086.
74. Aerts L, Holemans K, Van Assche FA. Maternal diabetes during pregnancy: consequences for the offspring. Diabetes Metab Rev 1990; 6:147–167.
75. Gauguier D, Bihoreau MT, Ktorza A, Berthault MF, Picon L. Inheritance of diabetes mellitus as consequence of gestational hyperglycemia in rats. Diabetes 1990; 39:734–739.