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FETAL PROGRAMMING AND GESTATIONAL DIABETES MELLITUS

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Abstract

Gestational diabetes mellitus is defined by new-onset glucose intolerance during pregnancy. About 2-5% of all pregnant women develop gestational diabetes during their pregnancies and the prevalence has increased considerably during the last decade. This metabolic condition is manifested when pancreatic β-cells lose their ability to compensate for increased insulin resistance during pregnancy, however, the pathogenesis of the disease remains largely unknown. Gestational diabetes is strongly associated with adverse pregnancy outcome as well as with long-term adverse effects on the offspring which likely occurs due to epigenetic modifications of the fetal genome. In the current review we address gestational diabetes and the short and long term complications for both mothers and offspring focusing on the importance of fetal programming in conferring risk of developing diseases in adulthood.

Keywords: gestational diabetes mellitus, fetal programming, epigenetics
1. Gestational Diabetes Mellitus- overview

Gestational diabetes mellitus (GDM) is defined by glucose intolerance of various degrees with first recognition during pregnancy [1-3]. In the USA, GDM affects up to 10% of all pregnancies and immediately after pregnancy, 5 to 10% of women with GDM are found to have type 2 diabetes mellitus (T2DM) [4]. Although GDM usually resolves within 6 weeks of delivery, approximately 50% of women diagnosed with this metabolic condition are expected to develop T2DM over 10-30 years [4,5]. Women with GDM experience an increased risk of developing other pregnancy complications, such as preeclampsia, and their offspring are at higher risk of developing short-term adverse outcomes such as macrosomia, neonatal hypoglycemia and neonatal cardiac dysfunction, and long-term complications, such as obesity, impaired glucose tolerance (IGT), and diabetes in adolescence or early adulthood [2,4,6].

During pregnancy, glucose metabolism changes to meet the nutritional demands of the mother and fetus [7]. It has been demonstrated that fasting glucose concentrations of women with normal glucose tolerance decreases as gestation progresses [8]. Although the mechanism is complex and still not well understood potential contributing factors have emerged, including: increased plasma volume in early gestation, increased glucose consumption due to increased feto-placental glucose intake in late gestation, and/or inadequate hepatic glucose production comparative to circulating glucose concentrations [3,7,8]. Nonetheless, despite the decrease in fasting glucose, hepatic glucose production is increased in normal pregnancy [7]. Insulin resistance occurs to some degree in all pregnancies [2,9]. In fact, by late pregnancy, women’s insulin sensitivity declines to one third in
comparison to their non-pregnant state. This increased insulin resistance facilitates
continuous glucose transfer to the fetus [10]. In order to maintain proper glucose
control, β-cell mass as well as the amount of insulin secreted from β-cells increases
during pregnancy [7]. Pregnant women who develop GDM, however, are unable to
increase insulin production to compensate for their increased resistance to insulin
[3,7,9,11].

GDM is considered to result from interaction between genetic and environmental risk
factors [12]. Studies have suggested that pregnancy triggers a series of metabolic
imbalances that lead to a diabetic state in some women who are already genetically
predisposed to develop diabetes [3]. Indeed, a study by Shaat et al, has identified a
variant in the transcription factor-7-like 2 (TCF7L2) gene to be associated with an
increased risk of GDM [13]. Furthermore, women with mutations in maturity onset
diabetes of the young (MODY) genes, with common variants in potassium inwardly-
rectifying channel subfamily J, member 11 (KCNJ11), glucokinase (GCK) and
hepatocyte nuclear factor-1alpha (HNF1α) have been demonstrated to be at higher
risk of developing GDM [12]. More recently, a two-stage genome-wide association
analysis in Korean women found genetic variants in the CDK5 Regulatory Subunit
Associated Protein 1-Like (1CDKAL1) gene and near the Melatonin Receptor 1B
(MTNR1B) gene to be strongly associated with GDM. Interestingly, they also provide
evidence that GDM and T2DM share a similar genetic background [14].

In addition, obesity or overweight, advanced maternal age, glycosuria, personal
history of GDM or a strong first-degree family history of T2DM and gestational
diabetes are important factors and warning signs which increase the risk of GDM
[3,15-17].
Numerous reports demonstrate the prevalence of GDM is increasing globally. Over the past 20 years, GDM has increased by approximately 10-100% [17-23], particularly in populations immigrating from less- to more-developed areas [24]. Population ageing, urbanization, obesity, sedentary lifestyles and stressful modern life are thought to be contributing factors in this emerging public health problem. In addition to adverse consequences for infants in the newborn period, GDM also contributes to the increasing incidence of diabetes and obesity in women with GDM and their offspring later in life [17,25]. Indeed, the Exploring Perinatal Outcomes among Children (EPOCH) study found that youth exposed to maternal GDM in utero had significantly higher average BMI over this range (p=0.01) and an accelerated BMI growth trajectory (p=0.008) compared with unexposed youth (Figure1) [26]. While all these factors are attributed to the epidemic of GDM, intrauterine exposures and gestational programming also play a role [25]. Coordinated efforts are required to provide better perinatal management and postpartum diabetes prevention strategies in order to alter these trends and to evade the ‘vicious cycle’ in which diabetes begets more diabetes.

2. GDM and perinatal programming

Fetuses exposure to maternal diabetes have a higher risk of abnormal glucose homeostasis in later life beyond that attributable to genetic factors [25,27,28]. Indeed, it is currently widely accepted that an abnormal in utero stimulus or ‘insult’ has the ability to disrupt the normal pattern of fetal development, permanently changing its body’s structure, physiology and metabolism, thereby, predisposing to chronic diseases in later life. This phenomenon is referred to as fetal or gestational
programming [28-32]. This hypothesis was first introduced by David J. Barker [29] who proposed “…that poor fetal and early post-natal nutrition imposes mechanisms of nutritional thrift upon the growing individual” leading to increased rates of future cardiovascular disease [33-35], hypertension [36-38], and T2DM [33,39]. Since the discovery that low birth weight is associated with increased risk of developing T2DM and the metabolic syndrome [33,39], numerous epidemiologic and experimental studies have confirmed these associations. In the current review, we will revise epidemiological studies that support the fetal programming theory and analyze the link between maternal diabetes and altered glucose homeostasis in the offspring. We will also discuss the possible cellular and molecular mechanisms behind this association.

2.1 Epidemiology and clinical observations of fetal programming

Dörner was among the first to provide epidemiological evidence that gestational diabetes or even slightly impaired glucose tolerance during pregnancy increases the risk of obesity and diabetes in offspring [40,41]. More direct evidence that adverse intrauterine environment might predispose to long-term T2DM came from a follow-up study of men and women from Hertfordshire, UK, in middle and later life whose body measures at birth had been recorded, showing, for the first time, that those who had had low birthweights presented increased risk of developing T2DM and impaired glucose tolerance in adult life [39]. When this theory was first proposed, it was regarded with much skepticism. The main criticism was that the sample selection was biased due to losses to follow-up owing to missing data on birth or incomplete identification. Other issues regarding the associations observed are potential confounding socioeconomic and environmental factors which could attribute to the
chronic diseases, *per se*, such that low birthweight alone might not be dictated as an independent risk factor. Notwithstanding, several other studies have confirmed this association [33,42-48], further suggesting that maternal undernutrition is able to permanently change insulin-glucose metabolism in the fetus, thus programming insulin resistance and T2DM in the offspring. These observations indicate that there is a linear inverse correlation between birthweight and T2DM. Nevertheless, *in utero* exposure to high glucose concentrations and to maternal diabetes, forces the fetus to increase its own insulin production, generally leading to excessively growth, a condition known as large for gestation age or macrosomic fetus [3,49]. Among Pima Indian Americans, a population with a particularly high prevalence of diabetes and obesity, it was reported, for the first time, that the prevalence of T2DM was greatest in those with the lowest and highest birthweights and the risk for subsequent diabetes among higher birthweight infants (over 4.5 kg) was entirely associated with maternal diabetes during pregnancy [45]. This demonstrates the importance of intrauterine exposure to impaired maternal glucose metabolism, even within a population that may have increased genetic susceptibility to T2DM. Further epidemiologic [50-52] and experimental [53,54] studies have demonstrated that high birthweight is associated with increased risk of T2DM in later life to the same extent as low birthweight. Taken together, these data indicate that, in fact, not a linear-inverse but a U-shaped relationship exists between weight at birth and future risk of developing T2DM and obesity (“diabesity”), with increased risk at both ends of the birthweight curve [31,32,45,51,52].

Given the increasing prevalence of “diabesity” among women of reproductive age in developed and Westernized developing countries, this may decisively contribute to the increasing frequency of high birth weight and therefore to greater diabetes
susceptibility in the offspring. Indeed, various studies have provided further evidence that offspring of mothers with uncontrolled diabetes, either pre-existing or originating during pregnancy, are 4-8 times more likely to develop diabetes in later life compared to those born from non-diabetic mothers. And a female born from a GDM pregnancy has a higher chance of developing GDM during her pregnancy, thus, creating a recurring disease cycle [55-57]. A way to counteract this tendency would be to avoid and/or adequately correct maternal overweight and/or maternal diabetes during pregnancy [17,25]. In line with this, a recent follow-up study of children of women un-treated versus treated for mild GDM demonstrated that treatment during pregnancy is associated with lower fasting glucose in female offspring at ages 5-10 years but not in male offspring. However, none of the children of treated or untreated mothers had diabetes at 5-10 years, suggesting that treatment of mild maternal diabetes may not affect childhood obesity or metabolic health [58]. Therefore, the possibility that fetal programming in the setting of maternal diabetes can have a beneficial offspring effect that can be modified by treatment remains unknown. Larger follow-up studies in pregnancy randomized trials are needed to provide evidence that the diabetes cycle can be interrupted.

2.2 Mechanisms

2.2.1 Pancreatic Development

Accumulated evidence points for a fetal developmental programming of later glucose metabolism dysfunction, however, the molecular mechanisms by which intrauterine exposure to hyperglycemia contributes to the development of obesity and diabetes are still not well understood. It is generally accepted that fetal programming results from a combination of mechanisms acting at organ, tissue, cellular and molecular
levels [32]. For example, current knowledge on the development of the pancreas in humans suggests that it may be particularly sensitive to an altered glucose and amino acid environment as it achieves complete development during late gestation and the perinatal period [29,32]. In fact, reduced β-cell mass was demonstrated in rat fetuses of hyperglycemic dams, with reduced expression of insulin-like growth factor 2 [59]. Moreover, as recently reviewed by Portha et al., the offspring of mild diabetic mothers, induced experimentally by streptozotocin (STZ) that selectively destroys β-cells, presented normal weight and enhanced percentage of pancreatic endocrine tissue, leading to higher β-cell mass. On the other hand, fetuses from severe diabetic dams were small at birth and had decreased pancreatic weight and degranulated β-cells, leading to low pancreatic insulin content and low plasma insulin. The long-term consequences evaluated in the progeny of these models revealed impaired glucose tolerance in the offspring of mild STZ diabetic rats due to lower insulin secretion in response to glucose, while insulin resistance was reported in the offspring of the severe STZ diabetic mothers [60]. Additionally, Hales et al. suggest that poor early development of islets of Langerhans and β-cells is a major factor in the etiology of T2DM [29]. Such alteration in the pancreas development, though, only compromise function later in life, when increasing physiologic requirements and over-solicitation of insufficient organ mass start to induce organ damage [32].

2.2.2 Placental role in GDM

The placenta fulfills several critical roles during pregnancy: not only is the regulator of materno-fetal transport of nutrients and gases but also a source of hormonal signals that influence maternal and fetal metabolism [30]. The placenta is in a continuous state of development throughout pregnancy with regulated periods of
branching angiogenesis, non-branching angiogenesis, trophoblast differentiation and syncytium formation [30]. Thus, when exposed to intrauterine adverse conditions, the placenta either changes the pattern of developmental (hormonal) signals to the fetus or the amount of nutrients/oxygen transported to the fetus [30,61] to such an extent that fetal development is altered, leading to long-term consequences throughout life [30,61,62]. The timing of the disruption of this development pattern is critical to determine the consequence on placental function and hence programming of the fetus [30,32].

Placentas from GDM pregnancies present characteristic histological features such as villous immaturity, villous fibrinoid necrosis, chorangiosis, and increased angiogenesis [63]. Generally, if impaired glucose metabolism is diagnosed in the early pregnancy, mainly structural dysfunctions are observed, whereas if detected in late gestation, GDM will affect placental function to a greater extent inflammation and oxidative stress that can lead to the chronic fetal hypoxia. Diabetic insults at the beginning of gestation instigates placenta adaptive responses to the diabetic environment, such as buffering excess maternal glucose or increased vascular resistance, which may lead to limited fetal growth. If the duration or extent of the diabetic insult, including maternal hyperglycemia, hyperinsulinemia, or dyslipidemia, exceeds the placental capacity to mount adequate responses, then excessive fetal growth may ensue [64]. Furthermore gene expression studies suggest that GDM is characterized by changes in trophoblast cells that include up-regulation of genes involved in a multitude of cellular functions including, immune response, organ development, regulation of cell death and also genes regulating inflammatory responses and endothelial reorganization reflecting a state of chronic systemic
inflammation of placentas of women with GDM that could ultimately lead to the chronic fetal hypoxia [65,66].

Fetal glucose production is minimal, therefore, the fetus depends almost completely on the maternal glucose supply. Since glucose is able to cross the placenta, fetuses from hyperglycemic mothers are inevitably predestined to grow in an environment of greater than normal glucose concentration [32]. The transplacental glucose flux follows as maternal-to-fetal concentration gradient and is handled by the transporter isoforms of the glucose transporters (GLUTs) family of proteins. It has been shown, however, that materno-fetal glucose transport is flow-limited and not regulated by transporter availability [61,62]. Indeed, recent observations in placenta perfusion studies found no difference in transplacental glucose transport between placentas from GDM and normal pregnancies at a fixed maternal-to-fetal glucose gradient [67,68]. Hence, these data indicate that the placenta is not involved in enhanced maternal-to-fetal glucose transfer in GDM and that the increased glucose flux across the placenta observed in GDM depends entirely on maternal-to-fetal concentration gradient [61,62]. Regarding the long-term effects of in utero exposure to a continuous range of high glucose concentrations throughout pregnancy, the Pedersen hypothesis is generally accepted. According to this proposition, maternal hyperglycemia increases glucose transfer to the fetus, thereby leading to fetal hyperglycemia, which in turn stimulates islet cell proliferation and insulin production [69]. This phenomenon generally leads to macrosomia, which has been associated with increased risk of later obesity and diabetes [70,71]. Moreover the overstimulation of fetal β-cells usually leads to hypertrophy of the tissue. This event, coupled to a higher fetal utilization of glucose could explain several abnormal structure and changes found in the newborn [69]. Indeed, the hyperglycemia and
adverse pregnancy outcome (HAPO) study suggested a positive linear correlation between maternal glucose and a range of adverse outcomes for the baby, including high birthweight and hypoglycemia [72].

2.2.3 Development plasticity and epigenetics

Many lines of evidence indicate that early life events play a powerful role in influencing later susceptibility to certain chronic diseases, such as T2DM, coronary heart disease, and hypertension. Despite all the explanations mentioned above, the molecular mechanisms through which the intrauterine exposure to hyperglycemia would translate into the development of diabetes are yet to be unraveled. An increased understanding on the developmental plasticity- defined as the ability of an organism to develop in various ways, depending on the particular environment [73], provides a conceptual basis to understand the association between fetal programming and adult disease. Developmental plasticity requires stable modulation of gene expression, and this appears to be mediated, at least in part, by epigenetic processes. In fact, accumulated evidence suggests that both the genome and the epigenome can interactively influence the phenotype determining sensitivity to later environmental factors and the subsequent risk of disease [74]. Recently published studies provide supporting evidence that epigenetic modifications may establish a better understanding on the mechanism whereby hyperglycemia influences T2DM in the offspring [75,76].

Although the genetic code of an organism is homogeneous, each individual cell type possesses its own gene-expression pattern that defines each cell’s biological fate. Stable alterations of this gene-expression profile are named ‘epigenetic’ modifications because they are heritable changes in gene expression without
alteration of the DNA sequence [77]. Most of these heritable changes are established during differentiation and are stably maintained through cell division, enabling cells to have distinct identities while containing the same genetic information [78]. DNA methylation and histone modifications are the best-known epigenetic mechanisms [79]. DNA methylation is the most extensively studied epigenetic signature [78] and it involves the covalent modification of cytosine residues that precede guanines- CpG dinucleotides, with the “p” referring to the phosphodiester bond between the cytosine and guanine nucleotides [80]. The CpG dinucleotides are not evenly distributed across the human genome but are instead clustered in CpG-rich regions known as CpG islands, spanning the 5′ regulatory end of many genes [78]. On the other hand, histone proteins which comprise the nucleosome core, contain a globular C-terminal domain and an unstructured N-terminal tail. The N-terminal tails of core histones can normally be altered post-translationally by a variety of modifications, including methylation, acetylation, ubiquitylation, SUMOylation and phosphorylation [78]. Histone modifications can function by changing the accessibility of chromatin or by recruiting and obstructing non-histone effector proteins, leading to either activation or repression depending upon which residues are modified and the type of modifications present. For example, lysine acetylation usually correlates with transcriptional activation, whereas lysine methylation leads to transcriptional activation or repression depending upon which residue is modified and the degree of methylation [78]. Epigenetic marks are mitotically stable but can also be subject to reprogramming in response to environmental stimuli such as changes in diet, physical activity, in utero environment, and pharmacological treatment [80]. Therefore, epigenetic signatures serve as a connection between life environment and phenotypes.
Although data in humans are still limited, accumulating evidence has provided insights into the involvement of epigenetic mechanisms in the developmental programming of obesity and T2DM later in life. A study of individuals who were prenatally exposed to famine during the Dutch Hunger Winter in 1944-1945 revealed, six decades later, lower DNA methylation of the imprinted insulin-like growth factor-2 (IGF2) gene, which has a role in growth and development, compared with their unexposed, same-sex siblings [81]. The same authors went on to further characterize DNA methylation, from whole blood, at 15 genomic loci harboring genes implicated in growth, development, and metabolic disease [82]. Again, adults who had been exposed to prenatal famine, exhibited altered methylation levels in the promoters of six of the chosen genes: DNA methylation of the interleukin 10 (IL10), leptin (LEP), ATP-binding cassette, sub-family A, member 1 (ABCA1), guanine nucleotide binding protein, alpha stimulating-antisense RNA (GNAS-AS), and maternally expressed 3 (MEG3) gene promoters was higher among individuals prenatally exposed to Dutch famine in comparison with their unexposed same-sex siblings [82]. Another report demonstrated an association between macrosomic babies and an increased placental methylation of the glucocorticoid receptor gene, which is a well-known candidate gene for obesity [83]. This study not only associates perinatal growth as a measure of the intrauterine environment with epigenetic alterations of the glucocorticoid receptor gene but also suggests a critical role for DNA methylation in determining placental function [83].

Recent studies have explored the role of epigenetics in offspring exposed to GDM. For instance, two candidate-gene studies of placental tissue, maternal circulating blood cells and cord blood cells from women with and without GDM, revealed that maternal glucose levels were associated with placental LEP [84], and adiponectin
methylation providing a potential link between maternal hyperglycemia, fetal programming and long-term risk of obesity. Another study compared the methylation pattern in peripheral blood leukocytes from non-diabetic adolescent Pima Indians who were either offspring of diabetic mothers or offspring of non-diabetic mothers. Using a methylated DNA immunoprecipitation (Me-DIP-chip) assay differential methylated regions were assayed and subsequent \textit{in silico} pathway analysis identified maturity onset diabetes of the young (MODY), T2D and Notch signaling as the top 3 enriched pathways with differentially methylated genes. These pathways include genes which are important in pancreatic development, $\beta$-cell response to glucose as well as insulin secretion [86], highlighting the potential impact of intrauterine hyperglycemia on methylation of genes implicated in $\beta$-cell function, thereby predisposing the offspring to increased risk of diabetes. Recently, a study using the 2-step epigenetic Mendelian randomization approach found that maternal glycemia is part of the causal pathways leading to higher leptin levels in cord blood with DNA methylation as a mediator of this association [87]. This study supports that maternal glycemia leads to epigenetic adaptations in the \textit{LEP} region of the offspring, potentially contributing to long-term programming of excessive adiposity later in life.

Although these studies provide exciting insights into possible epigenetic signatures that may contribute to long-term programming of obesity and metabolic disorders, one has to bear in mind that small samplings were included and these studies also lack of independent replication, hence the methylation changes detected often do not reach biological levels of significance.

It is relevant to mention that children whose mothers had diabetes during pregnancy are at increased risk of becoming obese and developing diabetes at young ages. Furthermore, many of these female offspring already have diabetes or abnormal
glucose tolerance by the time they reach their reproduction age, prolonging the cycle of diabetes [88]. There is some evidence that epigenetic and phenotypic traits induced by early life environment can be passed from one generation to the next [89], however, there is no evidence that it is the case for GDM.

3. Clinical aspects

As stated before, GDM is associated with short and long term complications, both for the mother and for the child. Fetal and newborn short-term complications include respiratory distress syndrome [90], prematurity, breech presentation [91], hypoglycemia, hyperbilirubinemia, macrosomia and death [92]. Macrosomia, defined as fetal weight over 4000g, is the most common fetal complication, and is associated with several perinatal adverse outcomes, such as acute fetal distress, birth trauma and emergency cesarean section [92]. In addition to these immediate risks, there are significant long-term risks of later life obesity, glucose intolerance, hypertension and cardiovascular disease in children of diabetic mothers [49].

The HAPO study has firmly established that maternal hyperglycemia, even at levels that do not meet the definition of GDM, is closely linked to macrosomia and excessive fetal growth [49] and also establishes a directly proportional relationship between maternal glycaemia and primary cesarean-section and neonatal hypoglycemia [72]. Also, treating milder hyperglycemia with lifestyle interventions and/or drug therapy, reduces mean blood sugar levels and improves outcomes. Two randomized trials using insulin have shown that glucose lowering strategies reduce birth weight, the proportion of large for gestational age infants, cesarean-section and perinatal morbidity [93,94]. Moreover, several publications about the use of oral
hypoglycemic agents, such as glibenclamide and metformin for the treatment of GDM [95-97], have shown the same results in terms of glycemic control or pregnancy outcomes compared with insulin. Even thought, treatment of GDM, whether with diet or with pharmacologic intervention, has shown to improve maternal and infant outcome in the short term, no long-term studies evaluating the impact of maternal glycemic control on the child’s future metabolic complications are available.

The current diagnosis of GDM is made during the late second trimester, which means the pathological state has already been established influencing the programming of the fetus.

Different testing strategies have been evaluated for diagnosis of GDM to improve maternal and infant health. A recent study by Farrar et al. has evaluated and compared different testing strategies for the diagnosis of GDM. For instance, when comparing 75-gram oral glucose tolerance test (OGTT) versus 100-gram OGTT, women given the 75-gram OGTT had a higher relative risk of being diagnosed with GDM, however there was insufficient evidence to allow assessment of which strategy is best for GDM diagnosis [98]. Furthermore, this trial did not evaluate when is the best timing during pregnancy to test women with GDM. The formal diagnostic criteria for GDM involve an OGTT at 24-28 weeks gestation. Different countries and organizations have different standards and cut-off points to define normal glucose tolerance and to define GDM but the International Association of Diabetes and Pregnancy Study Group (IADPSG) has recently determined new and lower thresholds, in the light of data indicating that glucose lowering strategies improve pregnancy outcomes even in women with mild glucose intolerance [93]. Although a glucose challenge test at 24-28 weeks is diagnostically robust, it has the disadvantage of being time consuming and difficult to extend to the whole
population. Another big disadvantage is the time during pregnancy when the test is performed, since it does not facilitate early management of GDM, exposing the fetus to a hyperglycemic environment for the whole of the first and part of the second trimester. This is important because there is evidence that fetuses exposed during early pregnancy to hyperglycemia had accelerated growth patterns from the first trimester onwards [99], highlighting the need for development of diagnostic models for GDM early in pregnancy to better stratify and predict risk of long term GDM-related complications and offer targeted intervention.

4. Conclusion and implications for prevention

Maternal diabetes is strongly linked to adverse pregnancy outcome, with clear evidence that exposure to maternal diabetes in utero has long term adverse effects on the offspring. This likely occurs due to epigenetic modifications of the fetal genome, and as such could be averted by therapy applied during pregnancy. Although treatment of extreme maternal hyperglycaemia improves pregnancy outcomes in the short term, the long term effects of treatment, and the threshold of maternal glycemia at which therapy is optimally applied is unknown. Further research is required to address both of these important issues. Possible topics of research that could help improve clinical GDM treatment and prevention of fetal programming are summarised in Table 1.
5. Acknowledgements

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6. References


Figure legend

Figure 1. Mean BMI curves for youth both exposed and unexposed to maternal diabetes in utero from 27 months of age to 13 years, adjusted for sex, race/ethnicity. Reprinted from The Journal of Pediatrics, Volume 158, Issue 6, Crume TL, Ogden L, Daniels S, Hamman RF, Norris, JM and Dabelea D, The Impact of In Utero Exposure to Diabetes on Childhood Body Mass Index Growth Trajectories: The EPOCH Study, Copyright (2011), with permission from Elsevier [26].
Effect of Exposure
Average BMI: p=0.01
BMI trajectory: p=0.008
Highlights

• Gestational diabetes prevalence is increasing globally.

• Fetal programming predisposes for future diseases in diabetic mothers and offspring.

• Need to establish perinatal management and postpartum diabetes prevention strategies.

• Long term complications could be predicted by early-pregnancy diagnostic models for GDM.