Foetal programming in a diabetic pregnancy: long-term implications for the offspring

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Maternal diabetes predisposes the growing foetus to non-communicable disease risk later in life. Studies show an increased risk of adiposity/obesity, type-2 diabetes and higher blood pressure in offspring of diabetic mothers. Altered metabolic and neuroendocrine functions, and epigenetic modification of genes involved in these functions are some of the mechanisms proposed for the offspring disease risk. Though optimal management of diabetes during pregnancy prevents its immediate complications, there is limited evidence on the influence of glycaemic control on long-term effects in the offspring. Future focus should be on prevention of pregnancy diabetes through appropriate maternal and child health policies in vulnerable populations.

Keywords: Gestational diabetes, non-communicable disease, offspring, pregnancy.

Introduction

TYPE-2 diabetes (T2D), hypertension, heart disease and other non-communicable diseases (NCDs), once considered to be disorders of old age are increasingly prevalent among young and economically productive age groups in the world[1]. With a rise in obesity and glucose intolerance among women of reproductive ages, the incidence of gestational diabetes mellitus (GDM) is also on the rise globally[2]. This is of particular concern because of its adverse consequences for the mother and the offspring. It has been long known that severe diabetes in the mother during pregnancy increases foetal congenital anomalies, and neonatal morbidity and mortality due to the direct effects of glucose on the developing embryo. Advances in diabetic treatment over the past few decades have reduced these immediate adverse effects to a large extent. However, offspring effects of lesser degrees of maternal hyperglycaemia such as large-for-gestational age and associated perinatal complications continue to pose significant public health problems. Recently, there has also been an increased focus on the long-term adverse associations of maternal diabetes on the offspring NCD risk.

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Maternal diabetes and foetal growth – fuel-mediated teratogenesis

It is well-known that maternal nutritional status is an important determinant of foetal growth. Maternal undernourishment has been shown to be associated with impaired growth *in utero* resulting in reduced size at birth[3]. On the other end of the spectrum, an over nourishment of the foetus associated with maternal obesity and diabetes usually leads to foetal overgrowth[4]. GDM, defined as 'any degree of glucose intolerance with onset or first recognition during pregnancy'[5], is the most prevalent form of diabetes during pregnancy, though an increasing proportion of women now have pre-existing type-1 diabetes (T1D) or T2D. Accelerated foetal growth is a common feature of diabetic pregnancies irrespective of the type of maternal diabetes.

Pregnancy is a diabetogenic condition. Gestational steroid hormones and placental lactogen induce peripheral insulin resistance and enhance foetal nutrition by diverting glucose, fatty acids and amino acids from maternal to foetal tissues[6]. Diabetes results when the pancreatic β-cells fail to cope with the increased demands for insulin. Maternal diabetes creates an environment of fuel-overload for the foetus, thus resulting in macrosomic and adipose phenotype described for newborns of diabetic mothers.

Jorgen Pedersen was one of the first to propose a mechanism underlying this enhanced foetal growth. In his classic 'hyperglycaemia–hyperinsulinism' hypothesis, he suggested that maternal hyperglycaemia results in foetal hyperglycaemia due to trans-placental transmission of glucose, and hence hypertrophy of foetal islet tissue and insulin hypersecretion[7]. He suggested that in diabetic pregnancies foetal weight and length increase directly by increased foetal glucose consumption as well as due to growth stimulating effects of foetal insulin. Subsequently, Norbert Frienkel[8] modified Pederson's hypothesis. He proposed that in diabetic pregnancies maternal fuels such as lipids and amino acids in addition to elevated glucose concentrations reach the foetus and stimulate the foetal pancreas and liver to secrete more insulin and insulin-like growth factors. As a result, foetal fuels are consumed more intensively leading to greater tissue anabolism and macrosomia. Freinkel postulated that this will have

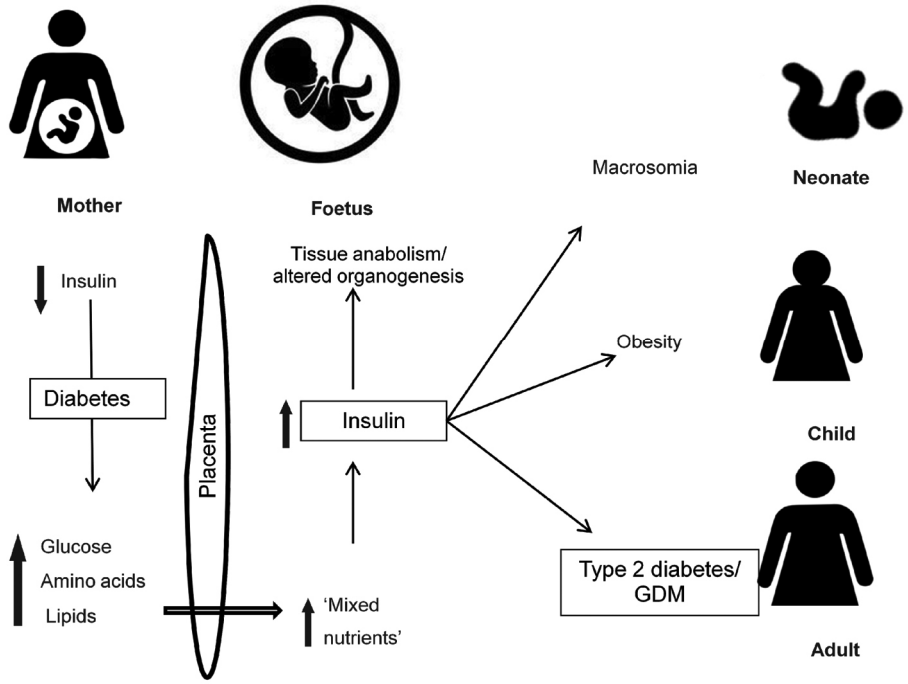

Figure 1. Fuel-mediated teratogenesis in diabetic pregnancies[8]. Transfer of excess of maternal 'mixed fuels' across placenta in diabetic pregnancies stimulates foetal hyperinsulinaemia. This results in greater tissue anabolism, neonatal macrosomia, and offspring adiposity and diabetes in later life.

long-lasting effects on the structure and metabolic functions of the foetus, and may cause obesity and diabetes in later life; this he termed 'fuel-mediated teratogenesis' (Figure 1).

Long-term effects of maternal diabetes – epidemiological evidence

The developmental origins of health and disease (DOHaD) hypothesis proposes that impaired nutrition during foetal development increases an individual's susceptibility to NCDs in later life[9]. This phenomenon is thought to reflect permanent effects of unbalanced foetal nutrition on structural and physiological systems (programming). This association was initially described by David Barker and colleagues for the foetal growth retardation presumably caused by exposure to intrauterine undernutrition[10]. They showed among UK adults that the prevalence of impaired glucose tolerance, T2D and coronary heart disease was highest in individuals with lowest birth weights. Recent evidence indicates that foetal overnutrition as in the case of maternal diabetes also programmes an individual to subsequent NCD development. The higher disease risk in offspring of diabetic mothers (ODM) underlies the *U*-shaped association between birth weight and T2D observed in some populations[11,12].

It has been well-recognized that maternal diabetes is a predictor of offspring diabetes later in life. Several studies have now demonstrated that ODM exhibit early obesity and develop glucose intolerance in adult life. Majority of these studies have been conducted among the Pima Indians of America, who are predisposed to high rates of T2D. Pima Indian studies showed that as early as between 5 and 19 years of age, ODM had higher rates of obesity than offspring of either non-diabetic or pre-diabetic mothers (mothers who developed diabetes after delivery), and had higher glucose concentrations[13,14]. By 20–24 years of age, 45% of ODM had developed diabetes, and over 70% had diabetes by 25–34 years of age[15]. These associations were independent of birth weight. Recent Pima Indian studies have also reported the development of other NCD risk factors such as higher blood pressure and impaired renal function in ODM[16]. The Pima Indian studies convincingly demonstrated that offspring associations were mainly due the intrauterine hyperglycaemic environment rather than genes or shared environment by showing that risks were considerably higher in ODM than offspring of diabetic fathers or pre-diabetic mothers[14]. Similarly, among siblings, those born after the diagnosis of mothers' diabetes were at a greater risk than their siblings born before[17].

Subsequently, several studies have examined the long-term effects of maternal diabetes in settings with lower incidence of the disease. They confirmed that the Pima Indian findings were applicable to other populations also. Silverman *et al.*[18,19] studied anthropometric characteristics and glucose and insulin metabolism in the US children born to mothers with GDM or pre-GDM. They

found higher obesity in ODM compared to control offspring by 6–8 years of age[18], and higher incidence of glucose intolerance by adolescence (19.3% vs 2.5% in controls)[19]. In another study from the US, Vohr *et al.*[20] proposed that size at birth was an important determinant for the development of obesity in ODM. They observed that large-for-gestational age ODM were likely to have higher body mass index (BMI), waist circumference and skinfold measurements between 4 and 7 years of age than large-for-gestational age controls or appropriate-for-gestational age ODM and controls. However, birth size was not a determinant of obesity in ODM in other studies. Majority of the above studies were conducted among children and adolescents, and therefore examined the intermediate risk factors for NCD development in ODM. Clausen *et al.*[21,22] examined the prevalence of glucose intolerance and metabolic syndrome in adults (18–27 years) born to mothers with mild GDM or T1D, and compared them with a background reference population with low diabetes susceptibility. They found that the prevalence of diabetes/pre-diabetes (21% and 11% respectively) and metabolic syndrome (24% and 14% respectively) was significantly higher in offspring of GDM or type-1 diabetic mothers than the reference population (4% and 6% respectively). Several cohort studies from different ethnic populations have now shown that offspring exposed to maternal diabetes exhibit higher rates of obesity, impaired glucose–insulin metabolism, metabolic syndrome and higher blood pressure[23–25]. Maternal diabetes has also been implicated in adverse psychological outcomes in the offspring, including lower psychomotor development and cognitive function[26]. Some researchers have also suggested a link between exposure to maternal diabetes and the development of schizophrenia[27].

Some studies have shown that variations within the normal range of maternal glucose alter foetal growth and increase the subsequent risk of obesity. Farmer *et al.*[28] had observed that fasting glucose concentrations of non-diabetic mothers increased all the neonatal measurements, particularly skinfolds. A continuous exposure even to a small excess of maternal glucose has been thought to induce chronic insulin stimulation and increase growth of insulin-sensitive adipose tissue and islet cells in the foetus. The Pune Maternal Nutrition Study (PMNS) of India also showed a continuous association between glucose concentrations in normoglycaemic pregnant women and neonatal birth weight and mid-upper arm and abdominal circumferences[29]. In Pima Indians, maternal 2 h glucose concentrations in the non-diabetic range were positively associated with relative weight of the offspring at 5–9 and 10–14 years of age, though it was not apparent at later ages[30]. The multinational Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO) study showed in a large group of non-diabetic pregnant women that there was a graded positive association between maternal glycaemia and neonatal adiposity[31]. However, there was no association between maternal glycaemia and children's adiposity at two years of age at one study centre in Belfast, UK[32]. The HAPO study further aims to explore associations of maternal glucose with long-term offspring disease risks in the absence of maternal diabetes.

There is now a renewed focus towards non-glucose-centric mechanisms of foetal programming, as originally suggested by Frienkel. In particular, maternal lipids have been thought to play an equally important role as glucose in foetal growth[33]. Pregnancy is associated with increased circulating lipids in humans, which intensify during obesity or GDM. Studies show that, as with GDM, obesity in the pregnant mother also potentially exposes the foetus to 'fuel-mediated teratogenesis'[25,34,35]. These effects have been thought to be mainly driven by circulating triglycerides and free fatty acids. Catalano *et al.*[34] showed that maternal obesity increases neonatal adiposity. The PMNS in India showed that the circulating lipids predict increased neonatal weight even in undernourished mothers[29]. These observations emphasize the need to explore the role of non-glucose fuels in foetal programming, especially in the light of findings in the offspring of normoglycaemic mothers.

Long-term programming effects of maternal glycaemia – evidence from India

There has been an escalating prevalence of T2D in India, with nearly 125 million people expected to develop this condition by 2040 (ref. 36). People of Indian origin develop diabetes at relatively younger ages compared to their western counterparts, and at lower levels of BMI threshold of obesity[37]. Programming by maternal undernutrition may be one of the factors driving the NCD epidemic in the country. Specifically, cohort studies in Pune and Mysore have shown that micronutrient imbalances are common among pregnant Indian women, and have proposed that intrauterine micronutrient deficiencies programme structural and functional aberrations and lead to higher disease risk in the offspring[38–40]. On the other hand, young women in India are also becoming increasingly adipose owing to rapid urbanization, resulting in high insulin resistance and glucose intolerance during pregnancy. The incidence of GDM is increasing among urban women, with an estimated prevalence of ~15% in urban populations[41]. More alarmingly, the Mysore Parthenon Study showed that micronutrient deficiencies and GDM may co-exist in the same women, thereby exposing their growing foetuses to multiple programming pathways[42]. Notwithstanding this, the long-term effect of maternal diabetes on offspring NCD risks has been little studied in India.

The initial evidence for a potential programming effect of maternal hyperglycaemia in India came from a birth cohort study at Holdsworth Memorial Hospital in

Mysore[43]. This study showed that adult men and women with T2D were more likely to be shorter and fatter (higher ponderal index) at birth and were born to women with higher weight and pelvic diameters. The researchers of this study suggested that these adults might have born to mothers with glucose intolerance. They hypothesized that widespread foetal growth retardation in India predisposes individuals to insulin resistance, and leads to glucose intolerance in pregnant women if exposed to obesogenic environments that accompany urbanization. Thus, maternal under nutrition results in diabetes in the next generation, and in case of female offspring, this results in GDM thus perpetuating the risk cycle.

Subsequently, the Mysore Parthenon Study, a purpose-designed prospective birth cohort study was established to examine the life-course predictors of NCDs, including maternal GDM[44]. The Parthenon study showed that, as expected, neonates of GDM mothers were heavier, longer and more adipose than control babies (offspring of non-GDM mother and non-diabetic father)[45]. There was a clustering of cardiovascular risk markers, including adiposity, higher glucose and insulin concentrations, insulin resistance (based on homeostasis model assessment for insulin resistance; HOMA-IR) and blood pressure in ODM during childhood and adolescence (Figure 2)[45–47]. The difference in subcutaneous adiposity between ODM and offspring of non-diabetic mothers continued to increase as the children aged (Figure 3). The Parthenon Study showed for the first time that maternal diabetes programmes neuroendocrine stress responses in the offspring, suggesting that this may be one of the pathways for their greater cardiovascular risk[47]. Even in the offspring of non-diabetic parents, both maternal and paternal insulin concentrations were positively associated with offspring adiposity and insulin resistance[45]. Thus in India, widespread maternal under nutrition with specific micronutrient deficiencies as well as high rates of gestational hyperglycaemia may programme offspring cardiometabolic disease risk, suggesting a dual teratogenesis[48]. This may add substantially to the country's diabetes epidemic.

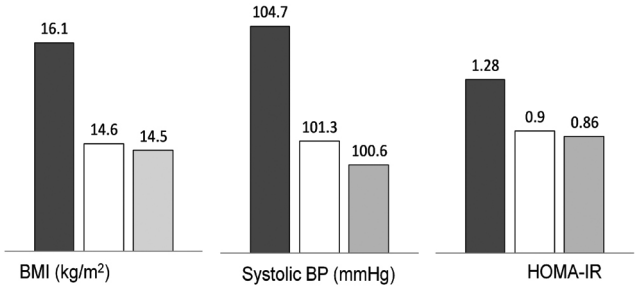

Figure 2. Mean body mass index, systolic blood pressure and HOMA-IR in the Mysore Parthenon Study offspring at 9.5 years (source: Krishnaveni *et al.*[46]). HOMA-IR, Homeostasis model assessment for insulin resistance. Dark grey bars: Offspring of diabetic mothers; open bars, Offspring of diabetic fathers; and light grey bars, control offspring.

Mechanistic explorations – animal model studies

The long-term programming of offspring cardiometabolic risk by maternal diabetes has been attributed to several mechanisms. Hyperinsulinaemia, secondary to early islet cell activation in the foetus has been proposed as an important factor underlying these associations. Aerts *et al.*[49] induced diabetes mimicking GDM in pregnant rats by injecting streptozotocin, and showed that altered fuel transfer to foetuses resulted in early islet hyperplasia, β-cell degranulation and depletion of insulin stores due to constant hyperglycaemia. Though β-cells appeared to recover post-natally, when challenged with glucose infusion, the endocrine pancreas failed to cope with the demand rendering the offspring hyperglycaemic. Different mechanisms were related to glucose intolerance in these rat offspring depending on the severity of maternal hyperglycaemia. Mild maternal diabetes was associated with foetal hyperinsulinaemia, and increased anabolism resulting in a deficient β-cell response in the adult offspring. Whereas severe maternal diabetes resulted in extreme hyperglycaemia, disorganized β-cell function and perinatal hypoinsulinaemia in the offspring. These offspring exhibited peripheral insulin resistance as adults. These studies showed that the diabetogenic tendency was passed onto subsequent generations mimicking genetic inheritance[50].

Perinatal hyperinsulinaemia has also been thought to have programming implications for neuroendocrine systems in the offspring. Animal studies suggest that hyperinsulinaemia during foetal development permanently alters the hypothalamic structure and function, thus programming the neurobehavioural pattern. Plagemann *et al.*[51] showed in rats that hyperinsulinaemia during critical periods of foetal development alters the expression and release of the neurotransmitter 'neuropeptide Y' in the hypothalamic centres that regulate appetite and body weight. The offspring rats tended to be hyperphagic, obese and hyperinsulinaemic. Leptin is an important

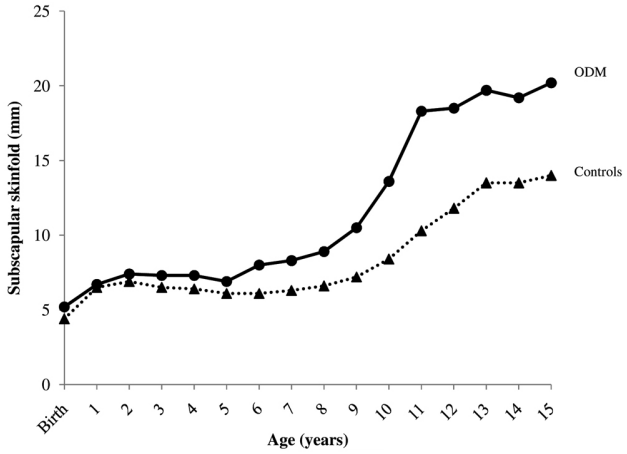

Figure 3. The Mysore Parthenon Study: mean subscapular skinfold thickness in offspring of diabetic mothers and control offspring from birth to 15 years of age.

hormone that regulates energy balance through its action on arcuate nucleus of the hypothalamus. Hyperinsulinaemia may induce leptin resistance and alter the leptin/insulin feedback system affecting the appetite regulation by the hypothalamus[52].

Some researchers also suggest the involvement of other mechanistic pathways, including oxidative stress, foetal dyslipedaemia and inflammation in the long-term programming for offspring NCD risks[53]. It has been shown in animal and human studies that maternal hyperglycaemia increases oxidative stress, and induces low-grade inflammation in the foetal cells[53]. These conditions result in impaired vascular development, endothelial dysfunction and aberrations in the neuroendocrine development and functioning.

Currently, there is a growing body of evidence suggesting that intrauterine exposure to hyperglycaemia induces epigenetic changes in several genes involved in metabolic functions. Epigenetic changes are heritable changes in gene expression without altering DNA sequence. Ruchat *et al.*[54] observed dysregulated DNA methylation levels in the obesity candidate genes LEP (leptin gene) and ADIPOQ (adiponectin gene) in placentae of diabetic pregnancies compared to the non-diabetic group. Maternal diabetes has also been shown to be associated with altered methylation levels for glucocorticoid receptor gene (*NR3C1*) in placenta and cord blood[55]. Intrauterine hyperglycaemia has been thought to trigger epigenetic changes in a number of gene pathways involved in energy metabolism and endocrine functions, and this has been proposed as a causal mechanism for NCD programming in the offspring[56].

Conclusion

In the backdrop of a global rise in the prevalence of obesity and glucose intolerance in pregnant women, maternal diabetes is all set to become a major public health problem, especially in emerging countries such as India. There is now strong evidence indicating that maternal hyperglycaemia creates a perturbed intrauterine environment and programmes the growing foetus for the risk of NCDs in later life. A meticulous glycaemic control has been shown to reduce the immediate effects of GDM on the foetus, including a reduced incidence of macrosomia[57]. The role of diabetes management in preventing the long-term NCD outcomes in the offspring is not known. There is some observational evidence to support that the offspring of untreated diabetic mothers are at a greater risk of obesity during childhood[58]. However, a recent randomized control trial of the treatment of mild GDM showed no reduction in offspring BMI at 4–5 years in the intervention group, though the treatment reduced the incidence of macrosomia[59]. This warrants further studies in this field. There is also an immediate need to shift the focus on ODM to recommend policies to incorporate the follow-up of ODM in maternal and child health practices. More importantly, devising measures to prevent the development of GDM through life-course approach is imperative to break the cycle of intergenerational transmission of NCDs in vulnerable populations.

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