Review

A Review of Fetal Development in Pregnancies with Maternal Type 2 Diabetes Mellitus (T2DM)- Associated Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation: Exploring Links to Pregestational Prediabetes

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A Review of Fetal Development in Pregnancies with Maternal Type 2 Diabetes Mellitus (T2DM)-Associated Hypothalamic-Pituitary-Adrenal (HPA) Axis Dysregulation: Exploring Links to Pregestational Prediabetes

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Abstract A growing body of research has identified fetal risk factors associated with adult diseases that form the basis for the Developmental Origins of Health and Disease (DOHaD) hypothesis. This theory proposes a critical developmental period during which the fetus is highly susceptible to specific environmental influences that significantly impact health from short to long term. Maternal stress and T2DM during pregnancy are among these influences, likely leading to fetal overexposure to glucocorticoids and suggesting a shared pathway between maternal dysregulated HPA axis and fetal environmental insults. Studies demonstrate that prenatal glucocorticoid exposure alters fetal HPA axis function, affecting brain function, tissue glucocorticoid availability, and fetal growth in utero. These programmed changes, such as altered HPA axis function and reduced fetal growth, contribute to metabolic disorders persisting into adulthood. T2DM is preceded by a prediabetic state, often asymptomatic, which shares similar pathophysiological complications with T2DM, including HPA axis dysregulation observed in animals. Therefore, investigating prediabetes during pregnancy alongside maternal HPA axis function and its effects on fetal outcomes is crucial, as these areas remain understudied. This review aims to synthesize existing literature on pre-existing T2DM during pregnancy, its links to fetal programming via HPA axis changes, and possible links to pregestational prediabetes.

Keywords: type 2 diabetes mellitus; prediabetes; pregnancy; maternal HPA axis; fetal HPA axis; programming; fetal development; placenta; glucocorticoids; metabolic diseases

1. Introduction

Fetal programming occurs during embryonic and fetal development, a vital stage during which tissues and organs are formed [1-3]. Many environmental cues, such as excess glucocorticoid exposure in utero, can contribute to various changes that include changes in molecular biological functions, such as receptor cell density or sensitivity, as well as alterations in metabolism or responses to physiological stressors [4, 5]. Essentially, fetal programming refers to the process of sustaining or affecting a stimulus or impairment that occurs at a crucial point in its development [6-8]. Studies show that maternal diabetes, particularly type 2 diabetes mellitus (T2DM), with increased glucocorticoid (GC) levels, may be one of the common mechanisms through which glucocorticoid insults exert their programming effects [9-11]. The rapid economic development and urbanisation, sedentary lifestyles and westernized diet has led to a rising burden of 463 million (20-79 years) adults living with T2DM in many parts of the world, especially in developing countries [12]. Although the weights of infants of diabetic mothers generally are skewed into the upper range, intrauterine growth restriction (IUGR), commonly diagnosed as low birth weight, occurs with concerning frequency in

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diabetic women, especially those with underlying, hypertension, uncontrolled blood glucose levels and vascular diseases [13-16]. T2DM has been shown to account for 30-50% of cases of pregestational diabetes during pregnancy [17].

Glucocorticoids (GC), such as cortisol in humans and corticosterone in rodents, are well known for their role in glucose homeostasis in adult life, especially during pregnancy, but have also been shown to be essential in fetal maturation [5, 18, 19]. However, fetal GC load is usually regulated by 11β-hydroxysteroid dehydrogenase type-2 (11β-HSD2), a placental enzyme that inactivates GCs [20, 21]. Increased maternal GC levels observed in T2DM and attenuating 11β-HSD2 expression—potentially increase fetal exposure to GCs, slowing fetal growth and altering the gestational period [22, 23]. Excessive glucocorticoid exposure in utero goes as far as altering the set-point and development of the offspring's HPA axis that alternately reprograms the HPA axis, thus compromising its function after birth [24-29]. In addition, excess maternal or fetal corticosterone causes the downregulation of fetal glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) and impairs the feedback regulation of the HPA axis in both infancy and adulthood [30-32]. Cross-sectional research has also indicated a connection between lower birth weights, elevated cortisol levels, catch up growth in neonatal period and adult obesity, which may be an indication of unfavourable adaptive responses till birth [30, 33-35]. The association between low birth weight was first reported several-fold increase in the incidence of glucose intolerance and T2DM in adult men compared with those born with normal birth weight [16, 36]. Furthermore, studies demonstrate that low birth weight has been associated with high risks of other non-communicable diseases (NCDs) such as hypertension, cardiovascular diseases and mental disorders in adulthood, correlating with the concept of Developmental Origins of Health and Disease (DOHaD) hypothesis [35, 37-39]. The DOHaD, which emerged as a broadening of the "Barker hypothesis" and was named for epidemiologist David Barker, explains the scenario in which *in-utero* maternal insults cause structural and functional alterations in fetal organs, extending postnatal life and increasing susceptibility to chronic disease in adulthood [40, 41].

Prediabetes is characterised by impaired glucose metabolism with glucose concentration above the optimal value but still below the diagnostic levels for T2DM [42, 43]. In 2019, the prevalence of prediabetes was 373.9 million with 15.3 % undiagnosed and it is expected to increase to 453.8 million by 2030 parallel with increasing T2DM prevalence [44, 45]. Studies show that prediabetes precedes T2DM and have been suggested that the onset of complications associated with T2DM begins during the prediabetic state including myocardial injury, renal dysfunction and activated the renin-angiotensin aldosterone system (RAAS), leaky gut and dysregulation in HPA axis function among others [46-51]. Literature primarily reports alterations that occur in pre-existing T2DM pregnancies and fetal programming, while the changes in maternal pregestational prediabetes HPA axis and it influence on the fetal HPA axis and development has not yet been explored. Therefore, in this review, we seek to review the existing literature on pre-existing T2DM in pregnancy-links to fetal programming with changes in their HPA axis as well as potential links to pregestational prediabetes-associated changes in the fetal HPA axis. The following section describes fetal programming, theories and disease associated.

2. Fetal Programming

According to Barker (1995), the early life environment affects fetal growth and adds to disease susceptibility [52, 53]. The developing baby adapts to an insult *in utero*, leading to long-term changes in form, physiology and metabolism that are beneficial for survival [40, 41]. Gluckman discovered that mismatches between early and later life circumstances might cause maladaptive alterations that raise the risk of a variety of cardiometabolic and psychiatric disorders as well as vulnerability factors pertaining to the phenomena known as fetal programming [54-56]. Fetal programming occurs when the normal pattern of fetal development is disrupted by an abnormal stimulus or 'insult' applied at a critical point in *in-utero* development [57-59]. According to the evidence for the Developmental Origins of Health and Disease (DOHaD) hypothesis, the antenatal period is a particularly vulnerable period of development in which exposure to adverse environments, such as glucocorticoid exposure,

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can have long-term or permanent effects on the offspring's health trajectory [60-62]. Studies have shown that maternal HPA axis is crucial during fetal development [18, 63]. However, maternal dysregulation in HPA axis during pregnancy or before pregnancy have been shown to exert it programming effect especially in the brain notably HPA axis [30, 64-66]. The following section details the physiological role of maternal HPA axis in pregnancy and role in fetal development.

1. Role of Maternal hypothalamic-pituitary-adrenal (HPA) axis in pregnancy

The hypothalamic-pituitary-adrenal axis is a complex system of neuroendocrine pathways and feedback loops that function to maintain physiological homeostasis through synthesis of glucocorticoids (GCs). Active GCs known as cortisol in humans and corticosterone in rodents [67-69]. The maternal HPA axis adapts during pregnancy and regulate stress-related deleterious effects on the mother and offspring [70, 71]. A non-diabetic pregnancy is a state of hyperactivity of HPA axis and of hypercortisolism especially towards late gestation [72-75]. The increased cortisol in late gestation is regulated by the placenta, an important source of secreting corticotropin-releasing hormone (CRH), which further enters the maternal pituitary gland via the hypophyseal portal circulation and enhances adrenocorticotropin (ACTH) synthesis and secretion into the peripheral circulation. ACTH increases the glucocorticoid synthesis and secretion through the adrenal cortex in the kidney into the bloodstream in the course of pregnancy [76-78]. GC levels influences the hypothalamic CRH in a negative feedback loop, while the placental CRH is strongly stimulated by GC in a mechanism of positive feedback loop [79, 80]. Despite the increasing circulating levels of GC, the diurnal secretion of cortisol is maintained throughout pregnancy [81]. In addition, studies show that high GC in pregnancy also play a primary role in regulating fuel homeostasis. After uptake of free cortisol from the circulation, cortisol increases availability of potential fuel substrates by mobilization of glucose, free fatty acids and amino acids through enhancing hepatic gluconeogenesis and glycogenolysis [82-85]. Hence, studies show that GC contribute to insulin resistance necessary to ensure that an adequate amount of glucose reaches the fetus for its growth and development [63, 86].

Moreover, the HPA axis is maintained through the glucocorticoids acting via two types of corticosteroid receptors in the brain glucocorticoid (GR) and mineralocorticoid (MR) receptors [87-92]. The expression of MR is confined primarily to limbic structures whereas the GR is more diffusely distributed with highest levels in the limbic system, the hypothalamic paraventricular nucleus (PVN) and in certain subfields of the hippocampus [93, 94]. In the brain, MR binds endogenous glucocorticoid with a higher affinity than GR and at basal concentrations of cortisol and corticosterone, MR are occupied while the GR remains largely unoccupied [95-97]. However, during periods of elevated plasma GC (i.e., during stress), there is increased occupation of the GR [98, 99]. In pregnancy, MR mRNA expression in the hippocampus is unaltered and GR gene expression is only modestly increased which promotes negative feedback maintaining HPA axis activity [19, 100]. Furthermore, studies show that in late pregnancy (the last week in the rat) is associated with a substantial reduction in HPA axis responses to both psychological and physical stressors in several species [100-102]. This adaptation is considered to buffer the impact of stress by reducing fetal exposure to maternal glucocorticoid, thus minimising the risk of detrimental glucocorticoid programming [19, 100, 103].

Furthermore, studies show that glucocorticoids, are lipophilic and can readily pass through the placental barrier by simple diffusion [104, 105]. Approximately 5-10 % of glucocorticoid that crosses, particularly in late gestation, plays a vital role in fetal organ development and maturation that includes neural mechanisms that mediate HPA axis development and adrenal function among others [18, 63]. However, one of the mechanisms that maternal protect the fetus from excess GC is through increasing the enzyme protective barrier in the placenta called 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) [93, 106]. This enzyme is found on both placental sides of the syncytiotrophoblast [106-108]. It metabolises active glucocorticoids (cortisol in humans and corticosterone in rats) into inactive glucocorticoids, thereby shielding the fetus against excessive glucocorticoid exposure from the mother [106-108]. Although the placenta metabolises a significant proportion of cortisol (80-90% during gestation), excess cortisol may reach the fetus and the 'barrier' can be further weakened by maternal high maternal glucocorticoid or placental dysfunction, which

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is commonly caused by increased oxidative stress resulting in hypoxia, allowing increased transfer of glucocorticoids from mother to fetus [19, 65, 109]. The HPA axis dysregulation with elevated basal glucocorticoid has been investigated in type 2 diabetes mellitus (T2DM) similarly to maternal stress and adverse fetal outcomes in pregnancy [9-11]. The HPA axis dysregulation with elevated basal glucocorticoid has been investigated in T2DM similarly to maternal stress and adverse outcomes in pregnancy [9-11]. Therefore, the following section describes T2DM, prevalences, pre-existing dysregulation in HPA axis function associated with fetal programming of the HPA axis and possible diseases associated in adulthood.

2. Changes in HPA axis in T2DM pregnancies associated with fetal programming.

T2DM accounts for 90-95% of all diagnosed diabetes mellitus (DM) cases and is regarded as a complicated and multifaceted illness caused by a mix of genetic and environmental risk factors [110, 111]. T2DM is characterised by insulin resistance and inadequate β-cell responsiveness to glucose stimulation [112, 113]. Globally, the International Diabetes Federation (IDF) estimated that by 2045, 629 million are expected to have T2DM [114]. The swift urbanization marked by the uptake of unhealthy, calorie-rich diets and sedentary lifestyles has played a role in the progressively rising prevalence of T2DM, particularly among females compared to males and the prevalence rises with age [115, 116]. While T2DM is often associated with macro-and microvascular complications, studies indicate that poor management of everyday stress in diabetic patients is also associated with constant activation and disrupted regulation of the HPA axis similar resemblance to maternal stress, accompanied by high levels of glucocorticoids [117]. Champaneri et al. similarly found high cortisol (hypercortisolism) levels throughout the day in diabetic women [118]. Established diabetes mellitus, either type 1 or 2, is the most common pre-existing medical condition in pregnant women in younger ages, resulting in an increasing proportion of pregnancies complicated by diabetes [119-121]. In some areas, pregnant women with T2DM now outnumber those with type 1 diabetes (T1DM) [122, 123].

The pathophysiology of fetal growth in the context of T2DM pregnancy is intricate and multifaceted [124, 125]. However, the complications of diabetes affecting the mother and fetus are well known [126-128]. Maternal complications include preterm labour, pre-eclampsia, nephropathy, microangiopathy, vascular diseases, caesarean section and postoperative wound complications, among others [129-131]. Fetal complications include fetal wastage from early pregnancy loss or congenital anomalies, macrosomia, shoulder dystocia, stillbirth and intrauterine growth restriction (IUGR), among others [13, 15, 16, 132, 133]. In addition, there are now a number of studies showing that pre-existing HPA axis dysregulated function high T2DM and maternal stressed pregnant women, measured in blood, saliva, urine, or amniotic fluid may induce epigenetic changes in the offspring's HPA function and contributing to causes of IUGR [80, 134-136].

Approximately 20% of pregnant women with diabetes experience gestational hypertension and/or preeclampsia [137]. The individuals most susceptible to these conditions are those who have pre-existing microvascular complications such as microangiopathy, hypertension, or inadequate control of blood glucose levels, which also contribute to endothelial dysfunction [137-139]. These complications have been shown to induce a reduction in trophoblast proliferation, delaying placental growth and development, particularly in the first few weeks of gestation [140]. This mechanism suggests a dysregulation of trophoblast invasion by the diabetic environment, leading to decreased placental perfusion resulting in placental dysfunction [141]. Studies show that placental dysfunction is associated with relatively low placental 11β-HSD2 activity therefore increasing active maternal GC to the fetus bloodstream [142, 143]. Overexposure to glucocorticoids during fetal development causes modifications in the expression of various cytostructural proteins, receptors, enzymes, ion channels, and growth factors [105]. These modifications result in changes in tissue structure, biochemical composition, metabolism, and hormone responsiveness, impacting the functionality of several fetal organ systems [142, 144]. Consequently, glucocorticoids trigger physiological processes that have little or may not have significant roles in utero but become crucial at birth, such as the HPA axis [105]. The HPA axis and its key limbic regulator, the hippocampus, are particularly sensitive to glucocorticoids and their perinatal programming actions [63, 145]. Studies show that glucocorticoids excess exposure during fetal development program specific effects in the brain, notably HPA axis,

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changing its development, sensitivity and activity *in utero*, relatively stressing its growth as the HPA axis begins to develop during the embryonic stage and continues to mature throughout pregnancy [31, 146, 147]. As a results, studies show that prenatal glucocorticoid exposure permanently increases basal plasma corticosterone levels in adult rats. This was because the density of both types of corticosteroid receptor, GRs and MRs, are permanently reduced in the hippocampus, changes anticipated to attenuate HPA axis feedback sensitivity [145, 148, 149].

In addition, studies show that fetal excess maternal GC exposure relative to early increases in the fetal GC concentration also trigger tissue differentiation and reduces accretion in the fetus [5]. As a result, the overall rate of maturation and growth declines as GC concentrations rise in fetus toward term and in response to adverse intrauterine conditions resulting in growth-retarded fetuses recognised as IUGR [142, 150-152]. The term intrauterine growth restriction (IUGR) refers to neonates whose birth weight and length fall below the 10th percentile for their gestational age [153, 154]. IUGR is a common antenatal diagnosis; nevertheless, some of these fetuses, particularly those who were not checked during pregnancy, may be discovered only after birth [153, 155]. The primary diagnostic criteria of IUGR include low birth weights (LWs), a surrogate marker of an adverse intrauterine environment and subsequent cardio-metabolic disease and mental health problems [156, 157].

On the other hand, the brain is heavily reliant on glucose for energy and mammals have redundant systems for controlling glucose production [158, 159]. As a result, it is possible that altered hypothalamus function may promote dysregulation of peripheral glucose metabolism, leading to insulin resistance or T2DM in adulthood [160, 161]. Research conducted by Hales et al. revealed a several-fold higher incidence of glucose intolerance and type 2 diabetes in adult men who were born with low birth weight as opposed to those who were born with normal birth weight, which established the first link between low birth weight and the development of T2DM [16, 36]. A study in rats showed that the smallest fetuses with the largest placentas had lower placental 11β-HSD2 activity and likely greater fetal exposure to maternal glucocorticoid [162] . Extrapolating from human studies, these were projected to have the highest adult blood pressures[20, 162]. Heightened HPA axis activity, particularly with increased ACTH and high plasma glucocorticoid levels, is seen in children and adults that were born underweight [163-166]. This happens in a variety of populations and precedes overt adult disease, particularly in socially disadvantaged communities such as the South African population [163, 167]. In addition, previous research has indicated that infants born with lower birth weights undergo catch-up growth within the initial two years of life [168-170]. This process is seen as a means to offset their genetically predetermined growth patterns [168-170]. Catch-up growth is also observed in other aspects of growth, such as changes in body weight and body composition [171, 172]. As per the theory of DOHaD the rapid catch-up growth experienced by low birthweight infants in their early years is associated with various metabolic conditions such as obesity, hypertension, cardiovascular diseases, metabolic syndrome and endothelial dysfunction later in adulthood [173-175]. Men were found to be more likely to develop cardiovascular disorders than women born with IUGR due to hormonal differences, as men had lower levels of oestrogen, which has protective effects on the circulatory system and may contribute to women's decreased risk of cardiovascular disease [176-178]. A prior study discovered that a combination of placental weight and birth weight predicts blood pressure and hypertension risk in men and women around the age of 50 [164]. People who were babies with large placentas had the highest blood pressure and a higher risk of hypertension [164]. Both The Barker and DOHaD hypotheses support these theories.

3. Prediabetes

Prediabetes is a condition in which blood glucose levels are abnormally high but do not meet the diagnostic criteria for type 2 diabetes mellitus (T2DM) [179]. Prediabetes can be identified by at least two of these characteristics: impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or high glycated haemoglobin A1c (HbA1c) [180, 181]. IFG patients have significant hepatic insulin resistance with normal skeletal muscle values and poor glucose suppression, which causes hyperglycemia during fasting due to impaired insulin secretion or reduced sensitivity of β-cells to glucose stimulation [180, 182]. IGT mainly impacts muscle insulin resistance, with minimal effects on

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liver insulin sensitivity. The reduced glucose absorption observed in individuals with impaired glucose tolerance (IGT) contributes to postprandial hyperglycemia [183, 184]. This is primarily due to pancreatic β-cell dysfunction, resulting in inadequate secretion of insulin to counteract elevated glucose levels and stimulate a response in insulin-targeted peripheral tissues [185-187]. Lastly, IFG Individuals have a poor early insulin response during the oral glucose tolerance test (OGTT) but improve insulin secretion during the second phase, which is one of the reasons why prediabetes is frequently undetectable [188-190]. As a result, the American Diabetes Association (ADA) recommendations were changed in 2003 to identify patients with prediabetes based on the following values: Fasting plasma glucose levels range from 5.6 mmol/L to 6.9 mmol/L, whereas IGT values recorded after OGTT range from 7.8 mmol/L to 11.0 mmol/L [191-193]. Glycated haemoglobin (HbA1c) levels between 5.7% to 6.4% are used as an additional diagnostic criterion for prediabetes [194-196]. Prior to the diagnosis of pre-diabetes, there is a presence of insulin resistance and malfunctioning of pancreatic β-cells [185-187]. Studies show that diet high in saturated fats, high in carbohydrates or high in fructose contribute to the development of intermediate hyperglycemia [197-199]. In addition, studies also show that these high caloric food leads to elevated triglycerides, increase release of free fatty acid (FFA) from adipocytes into circulation, which is accompanied by decreased FFA uptake by adipocytes in insulin-dependent tissues promoting insulin resistance and dyslipidemia [200-203]. These actions result in increased circulating FFA levels and FFA flux to the liver, which stimulates increased production and secretion of atherogenic very-low-density lipoprotein and small dense low-density lipoprotein particles and reduced high-density lipoprotein cholesterol (HDL-C) levels increasing risk of microvascular and macrovascular diseases [202, 203]. In addition, in the condition of insulin resistance, normal levels of insulin in the blood would be unable to elicit a reaction in the peripheral tissues that are targeted by insulin due to a decrease in the number of insulin receptors on the surface of cells, including muscle cells [204, 205]. With fewer receptors available, the cells become less responsive to insulin, reducing their ability to take up glucose [206]. Consequently, the β-cells of the pancreas react by producing additional insulin to counterbalance the increased glucose levels [207]. When the β-cells fail to secrete sufficient insulin to counteract insulin resistance, the blood glucose levels commence fluctuating leading to intermediate hyperglycemia and hyperinsulinemia leading to further alterations in β-cell function [208, 209].

3.1. Prevalence of Prediabetes

The prevalence of prediabetes has grown worldwide and in 2019, the International Diabetes Federation estimated the worldwide prevalence of prediabetes to be 373.9 million with 15.3 % undiagnosed according to studies [44, 45]. It is also projected that by 2030, approximately 453.8 million people will have prediabetes [210, 211]. The prevalence of prediabetes is anticipated to increase to 8.3% of the global adult population, equivalent to an estimated 587 million individuals by the year 2045 [212]. Studies show that prediabetes is frequently undetected due its often-asymptomatic nature in early stages hence most humans tend to unknowingly bypass the prediabetes stage to overt T2DM [213, 214]. In addition, studies show that the increase prediabetes prevalence is due to a rapid urbanization, increasingly sedentary lifestyles and unhealthy eating habits [215, 216]. As a result, a retrospective study in a rapidly urbanising area such as Durban, South Africa indicated that 68% of the individuals are prediabetic in the sample population between the ages of 20-45 years with 51.0 % of the study population being women [217]. This suggests that women of childbearing age are also affected by the global rise in prediabetes [218]. Furthermore, studies show that people with prediabetes have a 2 fold increase likelihood of developing T2DM [219, 220]. Moreover, studies show that complications of T2DM, are already evident in some people with prediabetes, these complications include myocardial injury, renal dysfunction and activated the renin-angiotensin aldosterone system (RAAS), leaky gut and dysregulation in HPA axis function among others [46-50].

3.2. HPA Axis Function in Prediabetes

Animal models have been observed to mirror human disease conditions, making them extensively utilized for studying physiological systems and human disease states [221-223]. A high

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fat high carbohydrate and 15% fructose diet-induced animal model of prediabetes has been found to mimic the human condition [224]. In addition, this animal model showed dysregulation in the functioning of the HPA axis in the prediabetic state as shown by elevated basal corticosterone and impaired regulation of their glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) in male prediabetic rats animals [225]. At present, there have been no investigations to show whether this phenomenon also exists in female prediabetic rats. Further, if present, this raised the question if maternal basal corticosterone and ACTH levels in prediabetic dams may impact fetal HPA axis development.

3. Possible links of prediabetes with T2DM pregnancies in association with HPA axis.

Both T2DM and prediabetes result from insulin resistance, leading to impaired glucose tolerance and chronic hyperglycemia [110, 111, 185-187]. Several studies have shown that during pregnancy, increased maternal serum glucocorticoids (GC) observed in T2DM and maternal stress may cross the placenta, overwhelming the protective placental barrier [13, 15, 16]. Conversely, research shows that pre-existing metabolic disorders associated with T2DM, such as hypertension, renal disease and maternal microangiopathy during pregnancy decreases trophoblast proliferation [226, 227] . This delays placental growth and its ability to supply the fetus with enough nutrients and oxygen, resulting in fetal hypoxia and inadequate nutrition supply [140]. Decreased placental function is linked to placental dysfunction and relatively low activity of placental 11β-HSD2 [142, 143]. These complications have been associated with increasing the vulnerability of the fetus during this period to unwanted programming effects such as increased transfer of active maternal cortisol to the fetal compartments [142, 143]. Early maternal GC exposure to the fetus has been associated with alterations to the balance of both GR and MR development in the fetal brain leading to changes in gene expression patterns and neural circuit formation evidenced by low GR and MR expression in offsprings after birth even in both basal and stressed animals [149, 228]. Moreover, studies showed that excessive GC exposure during critical periods of development can program the fetal HPA axis to be hyper-responsive beginning in utero persisting later in life such as prolonged increased in ACTH and GC seen in adulthood, potentially predisposing the offsprings to diseases such as depression, cardiometabolic or T2DM [64, 229]. Furthermore, studies suggest that excessive maternal GC exposure or reduced placental function during pregnancy is associated with reduced fetal growth contributing to intrauterine growth restriction (IUGR), commonly diagnosed at birth as low birth weight [131, 230]. Low birth weight offspring has been associated with HPA axis hyperactivity, glucose intolerance, hypertension, obesity and greater risks for developing depression, anxiety, T2DM and cardiovascular diseases in adulthood especially when there was catch up growth in the first 2 years supported by DOHaD hypotheses [60-62, 164].

There are various possible causes that contribute to IUGR or unfavourable hostile environment during pregnancy including preeclampsia, hypertensive disorders and these have been also associated with greater risk in T2DM pregnancies [231, 232]. Prediabetes, which often precedes the onset of T2DM, has been shown by various studies to be the genesis of complications associated with T2DM that include myocardial injury and renal dysfunction a recent study by Ludidi and colleagues showed that prediabetes is a risk factor for developing pre-eclampsia [233]. Since prediabetes often goes undiagnosed, this suggests that there is a population of people unaware of their elevated risk of developing hypertension and preeclampsia [233]. Therefore, the presence of prediabetes in pregnancy might increase the likelihood of IUGR and impaired glucose tolerance in offspring. With the increasing prevalence of prediabetes, especially in women of childbearing age, there is an increased possibility of pre-gestational, gestational and fetal outcome consequences. However, there have been no studies that have looked at how maternal prediabetes affects HPA axis along with fetal outcomes. Therefore, we recommend that future studies focus on pre-existing prediabetes in pregnancy, detailing its effects on maternal HPA axis function and its influences on fetal HPA axis development and offspring development.

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4. Conclusions

This review paper highlighted the significant impact of dysregulation of the maternal HPA axis during pregnancy, particularly elevated glucocorticoid levels, on fetal growth and programming, with potential implications for HPA axis development in the fetus seen in T2DM. It discussed the possible links between prediabetes and T2DM pregnancies relative to impaired HPA axis function. However, further research is needed to understand the effects of pregestational prediabetes on maternal HPA axis and its impact on fetal outcomes. This could further underscore the importance of continued investigation into the complex interplay between maternal metabolic health, HPA axis regulation and fetal development to inform clinical management and improve pregnancy outcomes.

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