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Review

Gestational Diabetes and the Spectrum of Congenital Cardiac, Neural, and Limb Anomalies

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ABSTRACT

Gestational Diabetes mellitus (GDM) is a common metabolic disorder of pregnancy, characterised by gestational hyperglycaemia resulting from inadequate insulin secretion and increased insulin resistance. GDM poses significant short- and long-term health risks for both mothers and their offspring. Emerging evidence highlights the transgenerational impact of maternal hyperglycaemia, linking the intrauterine metabolic environment to long-term alterations in offspring health. Children born to mothers with GDM are at increased risk of developing metabolic disorders, including obesity, insulin resistance, and Type 2 Diabetes mellitus, as well as adverse neurodevelopment outcomes and cardiovascular abnormalities. This review synthesises current evidence on the pathophysiological mechanisms underlying these associations, including foetal programming, epigenetic modifications, and altered placental function. Understanding the intergenerational consequences of GDM is critical for developing preventive strategies and targeted interventions to mitigate long-term health risks in both mothers and their children.

KEYWORDS: Gestational diabetes mellitus (GDM), Congenital anomalies, Congenital heart defect, Neural tube defects, Congenital limb deficiencies, Maternal hyperglycaemia, Fetal programming, Oxidative stress, Epigenetic mechanisms

INTRODUCTION

A congenital abnormality is defined as a deviation in structural development occurring during the prenatal period, encompassing both gross and microscopic changes that differ markedly from the normal reference population[1]. Such abnormalities are classified as major when they result in, or are expected to result in, considerable impairment of health, function, or survival. Congenital abnormalities may originate at multiple points along early development, ranging from genetic recombination during gametogenesis to disruptions in embryogenesis, organ formation, or later stages of foetal development[1,2].

Malformations can be categorised according to pathogenetic, clinical, and etiological frameworks. When considered from an etiological viewpoint, these conditions are broadly grouped into primary forms, arising from genetic determinants, and secondary forms, resulting from environmental influences such as chemical or physical exposures, metabolic or nutritional disturbances, vascular disruptions, and mechanical factors[3]. Accordingly, congenital anomalies may stem from a single

cause, involve multiple contributing factors, or, in some cases, lack an identifiable origin.

From a clinical perspective, anomalies are categorized as either major or minor. Major malformations represent substantial deviations in structure, appearance, or function and often require medical or surgical intervention; examples include neural tube defects and orofacial clefts. In contrast, minor malformations, such as clinodactyly or bifid tongue, generally do not produce serious functional impairment or threaten survival[4]. From a pathogenetic perspective, congenital malformations can be grouped into syndromes, in which a single cause results in several related structural defects; associations, where multiple anomalies occur together without a known common cause; and dysplasia, which involve abnormal development or structure of specific tissues[3].

A glucose intolerance that is initially identified during pregnancy but does not meet the criteria for Type 1 or Type 2 Diabetes is known as gestational *Diabetes mellitus*[5]. Exposure to maternal GDM has been associated with a range of short- and long-term adverse outcomes in offspring. The possibility of congenital abnormalities in children exposed to maternal GDM is one contentious consequence of GDM. In contrast, pre-gestational *Diabetes mellitus* (PGDM), including both Type 1 and Type 2 Diabetes, has long been established as a risk factor for congenital heart defects. Nevertheless, existing evidence regarding the association between maternal PGDM and specific congenital heart defects, as well as abnormalities involving the musculoskeletal, nervous, genitourinary, and gastrointestinal systems, remains inconsistent. Consequently, further well-designed studies are required to better define these relationships. Similar to Pre-gestational *Diabetes mellitus*, Gestational *Diabetes mellitus* exerts substantial effects on maternal health and on offspring outcomes during pregnancy, childbirth, and the postnatal period. An increasing number of studies have sought to evaluate the risk of specific categories of congenital anomalies among children born to mothers with GDM[6,7]. However, evidence regarding the influence of maternal Diabetes on less common or non-cardiac congenital anomalies remains limited, as most previous meta-analyses have primarily focused on associations between maternal Diabetes and congenital heart defects in offspring[8,9].

This review seeks to integrate existing evidence and highlight key knowledge gaps to guide future investigations about the association between gestational *Diabetes mellitus* and congenital abnormalities. From both clinical counselling and public health perspectives, robust and comprehensive estimates of the risk of specific congenital anomalies associated with maternal Diabetes are essential.

Pathophysiological Mechanisms Linking Maternal Diabetes to Altered Foetal Development

Gestational *Diabetes mellitus* (GDM) is a disorder of glucose regulation that is first identified during pregnancy[10]. Pregnancy is associated with increased production of hormones such as prolactin, oestrogen, and placental lactogen, which facilitate nutrient transfer from the mother to the foetus while reducing maternal insulin sensitivity to prevent hypoglycaemia. Insulin resistance typically emerges in mid-gestation and progressively intensifies as pregnancy advances. To compensate for the diabetogenic effects of placental hormones, maternal pancreatic β-cells normally increase insulin secretion, sometimes up to threefold. When this adaptive response is insufficient to meet the rising metabolic demands of late pregnancy, maternal blood glucose levels increase, leading to foetal hyperglycemia and a compensatory increase in insulin secretion by the foetal pancreas[11].

Chronic elevation of maternal blood glucose represents the fundamental metabolic disturbance in Diabetes and initiates a cascade of intracellular processes that have been implicated in abnormal foetal development[12]. One widely recognized pathway contributing to Diabetes-related complications involves excessive production of mitochondrial superoxide, leading to disruption of cellular redox balance[12] Hyperglycaemic conditions promote the accumulation of reactive oxygen species (ROS), which play a central role in diabetic pathophysiology, and increasing evidence suggests that such oxidative stress interferes with tightly regulated events during embryogenesis[12,13]. Rather than inducing direct DNA damage, oxidative stress appears to modify the transcriptional regulation of genes critical for developmental progression. The degree to which individual genes are affected depends on their sensitivity to glucose-induced alterations in the intracellular redox environment, thereby influencing susceptibility to congenital anomalies in the developing foetus[12].

In parallel, alterations in cellular energy sensing pathways have been linked to Diabetes-associated teratogenic effects. AMP-activated protein kinase (AMPK), a key regulator activated by rising intracellular adenosine monophosphate levels, has been proposed as an important mediator in this process [14,15].Beyond its role in metabolic homeostasis, activated AMPK translocates to the nucleus and modulates the activity of several regulatory proteins, including hypoxia-inducible factor-1α. Disturbance of this signalling axis may impair normal developmental signalling pathways and contribute to the emergence of congenital abnormalities[12].

Comparative Risk of Overall Congenital Anomalies in Offspring of Women with Pre-Gestational Versus Gestational *Diabetes Mellitus*

The likelihood of congenital anomalies is greater among offspring of women with pre-gestational *Diabetes mellitus* (PGDM) compared with those born to mothers with gestational *Diabetes mellitus* (GDM). Embryonic development begins at fertilization, with critical stages of organ formation occurring primarily between the third and eighth weeks after conception

and continuing throughout gestation. Consequently, the first trimester represents a particularly vulnerable period for normal organ development. In pregnancies complicated by PGDM, prolonged exposure to elevated glucose levels may occur before conception and persist into early gestation, thereby disrupting key developmental processes and increasing the risk of congenital anomalies[16].

In contrast, GDM is most commonly identified during mid-pregnancy, typically between 24 and 28 weeks of gestation[16]. As a result, maternal glucose concentrations during early pregnancy are often within normal limits or only mildly elevated, limiting their impact on early organogenesis. This temporal difference in glycaemic exposure may partly account for the lower incidence of congenital anomalies observed in offspring of women with GDM compared with PGDM. Nevertheless, many women who later develop GDM exhibit underlying metabolic abnormalities prior to pregnancy, including impaired pancreatic β-cell function and heightened insulin resistance[17,18]. These pre-existing disturbances may predispose to hyperglycemia during critical developmental windows and contribute to an elevated risk of malformations, although further investigation is required to clarify the mechanisms involved.

Congenital Heart Defects

Cardiac activity begins early in embryonic life, with the primitive heart initiating rhythmic contractions approximately three weeks after fertilization, making it the earliest functioning organ. Structural partitioning of the heart, including formation of the interatrial septum, occurs predominantly between the fourth and seventh weeks of gestation. During this critical developmental window, exposure to elevated glucose levels appears to exert a greater disruptive effect on cardiac morphogenesis than hyperglycemia occurring later in pregnancy[19].

A recent systematic review and meta-analysis by Chen et al., incorporating data from 24 population-based and 18 hospital-based studies, demonstrated a significant association between maternal gestational *Diabetes mellitus* and an increased risk of most congenital heart defect phenotypes[8]. Mechanistically, hyperglycemia has been shown to suppress embryonic expression of paired box gene 3 (PAX3), leading to upregulation of the tumour suppressor protein p53. Increased p53 activity promotes apoptosis within developing cardiac tissues, particularly affecting ventricular septation, and may contribute to the development of congenital cardiac malformations[20,21].

In summary, foetal outcomes following exposure to maternal hyperglycemia are influenced by multiple interacting determinants. These include the timing of exposure relative to key stages of development, the degree of glycaemic disturbance, the presence of coexisting maternal conditions or additional risk factors, and the underlying genetic makeup of the foetus. Together, these factors may drive epigenetic modifications and complex biological interactions that ultimately affect cardiac development in the fetus[22,23].

Neural Tube Defects

Early embryonic nervous system formation, termed neurogenesis, involves the proliferation and folding of neuroepithelial cells to form the neural tube, which later develops into the central nervous system (CNS)[24]. Disruption of neural tube closure results in neural tube defects (NTDs), severe structural congenital anomalies that significantly contribute to infant morbidity and mortality. NTDs represent the second most common category of birth defects after congenital heart disease[25].

Worldwide, the prevalence of NTDs varies considerably, ranging from approximately 0.5 to 10 per 1,000 births, with an estimated 300,000 to 500,000 affected pregnancies reported annually[26]. Although genetic factors play a role, the majority of NTDs arise from non-genetic causes. Among these, maternal Diabetes has emerged as one of the most prominent and increasingly prevalent risk factors[27].

Hyperglycemia during pregnancy initiates multiple cellular stress responses in the developing embryo, including mitochondrial impairment, oxidative stress, and endoplasmic reticulum stress. These disturbances disrupt normal signalling pathways and gene regulation within neural tissues, promote excessive programmed cell death in neural folds, and ultimately increase the likelihood of neural tube defect formation[28,29,30].

According to study conducted by LijunCao et al., oxidative stress brought on by hyperglycaemia initiates neural tube cell death and stimulates apoptotic JNK1/2 signal transduction, suggesting that targeted deletion of the JNK1 gene can alleviate Diabetes-induced NTD[31].

Congenital Limb Deficiencies

Congenital limb deficiencies are relatively rare conditions that adversely affect an individual's functional abilities and overall quality of life. These anomalies are classified into five groups: transverse defects, intercalary defects, mixed defects, longitudinal defects (including preaxial, postaxial, and cleft types), and an unclassified group for cases that cannot be clearly categorized[32]. Klungsoyr and colleagues[33] reported that pregestational Diabetes increases the risk of limb deficiencies by approximately three times. Data from the National Birth Defects Prevention Study (NBDPS) further support this association, with Correa et al.[34] demonstrating a six- to seven-fold higher risk of longitudinal limb defects in the presence of pregestational Diabetes, and Dukhovny et al.[35] identifying about a five-fold elevation in risk for limb deficiencies overall.

DISCUSSION

Both Pre-pregnancy Diabetes and gestational *Diabetes mellitus* (GDM) are characterized by hyperglycemia; however, in GDM, abnormal glucose regulation usually becomes

apparent or is diagnosed only during the second trimester[1]. Research on Pre-gestational Diabetes has consistently demonstrated a strong association between maternal hyperglycemia and a higher occurrence of severe congenital anomalies in offspring, with hyperglycemia recognised as a major teratogenic factor. In addition to elevated glucose levels, increased production of reactive oxygen species may further contribute to the risk of congenital anomalies in pregnancies affected by Diabetes[12].

During normal pregnancy, metabolic adaptations such as increased insulin resistance and compensatory beta-cell proliferation occur. In women with GDM, pre-existing insulin resistance is often present, which may limit adequate beta-cell expansion and lead to hyperglycemia during pregnancy. Nevertheless, the precise biological mechanisms underlying this association remain incompletely understood[11].

Evidence from the literature suggests an association between gestational *Diabetes mellitus* (GDM) and an increased occurrence of chromosomal abnormalities. Moore et al., in a study based on amniocentesis findings, reported a higher frequency of chromosomal anomalies among pregnancies complicated by GDM, with a notable predominance of sex chromosome abnormalities[36].

These observations are further supported by population-based data from Jenni Kinnunen and colleagues, who conducted comprehensive GDM screening and demonstrated a greater likelihood of chromosomal abnormalities in offspring of mothers with GDM. Given that GDM is most often diagnosed during the second trimester, it is unlikely to act as a direct causal factor for congenital or chromosomal anomalies. Instead, GDM may serve as a clinical marker of underlying, long-standing maternal metabolic disturbances that exert their effects during meiosis and the earliest phases of embryonic development[1].

Available evidence indicates that pregnancies complicated by maternal Diabetes carry an approximately threefold higher risk of congenital heart disease (CHD) compared with pregnancies in nondiabetic women. Among the spectrum of congenital anomalies linked to maternal Diabetes, CHDs represent the most commonly reported category[37]. Nevertheless, considerable variability exists across studies regarding the magnitude of this association, and the specific relationships between maternal Diabetes and individual CHD subtypes remain incompletely defined. The range of cardiac defects described is broad, encompassing more than 20 distinct phenotypes. Despite this heterogeneity, certain lesions, such as conotruncal abnormalities, atrioventricular septal defects, ventricular outflow tract obstructions, and double-outlet right ventricle have been more consistently reported in association with maternal Diabetes[38,39,40].

Maternal Diabetes has been consistently implicated in the development of major congenital anomalies, particularly those affecting the nervous and musculoskeletal systems. Disruption of early embryonic processes, such as neural tube formation during neurogenesis, can result in neural tube defects (NTDs), which are among the leading causes of infant morbidity and mortality worldwide and rank second only to congenital heart disease in frequency. Experimental and clinical evidence indicates that hyperglycemia-induced cellular stress, mediated through oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress, and aberrant apoptotic signalling, plays a central role in disturbing normal neural development and increasing the risk of NTDs. In addition to neural anomalies, maternal Diabetes is strongly associated with congenital limb deficiencies, which, although uncommon, have significant functional and quality-of-life implications. These defects encompass a broad spectrum of phenotypes, including transverse, intercalary, mixed, longitudinal, and unclassified forms[25,31,32].

Collectively, these findings highlight the profound influence of maternal glycaemic status on early embryonic development and underscore the importance of optimal metabolic control to reduce the burden of severe structural birth defects.

Early screening and close surveillance for gestational *Diabetes mellitus* (GDM) play a crucial role in timely detection and appropriate management. Commonly used approaches include the glucose challenge test, measurement of HbA1c, continuous glucose monitoring, ultrasonography, and antenatal non-stress testing, while confirmation of the diagnosis relies on the oral glucose tolerance test. Several strategies have been proposed to reduce the adverse impact of GDM on foetal and neonatal outcomes. These primarily involve medical nutrition therapy, supplementation with probiotics, and pharmacological treatment when lifestyle measures are insufficient. Insulin therapy remains the treatment of choice, as it does not cross the placental barrier. Although oral hypoglycaemic agents may be considered in certain settings, their routine use is discouraged because glyburide has been associated with unfavourable neonatal effects, and metformin is known to cross the placenta and reach the foetus. Incretin-based therapies may influence glucose regulation either directly or via insulin activation; however, their overall benefit in GDM appears to be limited[41].

CONCLUSION

Gestational *Diabetes mellitus* represents more than a transient metabolic disturbance of pregnancy; it is a marker of maternal metabolic vulnerability with far-reaching consequences for foetal development. Although the risk of congenital anomalies is substantially higher in pre-gestational Diabetes, growing data suggest that GDM reflects pre-existing metabolic dysfunction that may influence embryogenesis during critical developmental windows. Mechanistic pathways involving oxidative stress, disrupted energy sensing, altered gene regulation, and apoptosis provide biological plausibility for these associations. Importantly, effective screening, early identification, and optimized glycaemic control remain central to reducing adverse foetal outcomes.

Future research should prioritize standardized diagnostic criteria, longitudinal assessment of metabolic health before and during pregnancy, and deeper exploration of epigenetic and placental mechanisms linking maternal glucose dysregulation to foetal development. A clearer understanding of these pathways will be essential for refining preventive strategies and improving long-term outcomes for both mothers and their offspring.

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