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Review Article

Cardiometabolic Risks in Gestational Diabetes Mellitus: A Mini-Review

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ABSTRACT
Diabetes is one of the most common medical problems encountered in about 3.8% - 41% of pregnancies across the various parts of India. It contributes to maternal morbidity and mortality, especially in developing countries. Insulin resistance and β – cell dysfunction are the characteristics of GDM. Women with GDM had many immediate adverse fetomaternal and neonatal outcomes. In addition to the immediate adverse outcomes, women with GDM also had long-term complications such as dyslipidemia, metabolic syndrome, hypertension, type 2 diabetes, cardiovascular disease in later life. Current evidence suggests that GDM is highly associated with cardiometabolic risks (CMR) during gestation and in post-gestational period. Though the mechanism behind the pathogenesis of CMR in GDM is multifactorial, placental hormones, inflammation, endothelial dysfunction and oxidative stress play a significant role in the pathophysiology of cardiovascular risks in pregnant women with GDM.
Key words: Gestational diabetes mellitus, Insulin resistance, Dyslipidemia, Cardiometabolic risks, Inflammation, Endothelial dysfunction.

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INTRODUCTION

Gestational Diabetes Mellitus (GDM) is a common metabolic disorder during pregnancy[1] and is a severe public health problem as it is linked to an increased threat of perinatal death and morbidity.[2] GDM has been more common in recent decades, coinciding with older age at conception and cosmopolitan cultures, as well as an economic boom. Ischemic heart disease and type 2 diabetes are also linked to GDM.[3-4] Children of mothers with GDM are more prone to cardiometabolic problems later in life.[5] According to a meta-analysis, the prevalence of GDM in Asia was 20.9 percent,[6] with 14.8 percent in China.[7] The prevalence of GDM has been on the rise in recent years.

Abnormal carbohydrate tolerance occurs with the onset or first detection during the present pregnancy, which commonly manifests during mid-pregnancy at around the 24th week of gestation. The abnormality is due to the inability of the pancreas to increase insulin secretion as a response to the progressive insulin resistance that occurs typically at the later stages of gestation. International Diabetes Federation suggests that 1 in 6 pregnancies are affected by diabetes with a prevalence rate of 16%.[8] Increased maternal age (especially, >35 years old), pre-pregnancy BMI, history of GDM in previous pregnancies and family history of DM increases the prevalence of GDM.[9] Although glucose intolerance resolves after delivery in majority, they exhibit an increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD). Women with history of GDM have a sevenfold increased risk of developing T2DM, with 20-70% risk in the first decade after delivery.[10] Therefore, GDM is an established clinical predictor of future risk of diabetes, and affected women are more than seven times more likely to have type 2 diabetes than women of their age. Many studies have shown that women with GDM have a higher incidence of cardiovascular events postpartum. However, these studies have produced different results regarding whether this risk is reliant upon the concurrent onset of type 2 diabetes and have provided varying estimates of its magnitude. Some studies suggest that women with GDM develop cardiovascular disease only if they progress to type 2 diabetes,[11-12] while other studies claims that even in the absence of diabetes, increased risk may appear.[13] Thus in this article, we have reviewed the concept, mechanism and effects of GDM and its possible link to cardiometabolic risks (CMR). Also, we have suggested possible methods for preventing the development of CMR in women suffering with GDM.

BASIC ETIOLOGY OF GDM

The limited peripheral insulin sensitivity in pregnant women who are not hyperglycemic prior to conception is associated with GDM during late gestation.[14] As a result of the ability of pancreatic β-cells to increase insulin response in early

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pregnancy, these women individually achieve normoglycaemia, whereas during late pregnancy, insulin resistance increases.[15] The aetiology of GDM includes both impaired β-cell function and tissue insulin resistance because GDM often results from β-cell dysfunction on a background of persistent insulin resistance throughout pregnancy.

Neurohormonal regulators of GDM are adipokines such as leptin and adiponectin, which regulates appetite, active energy expenditure, basal metabolic rate and it is made of network of central and peripheral signals.[16-17] These contribute to GDM by influencing maternal adiposity and utilization of glucose.

FETOMATERNAL OUTCOMES IN GDM

Adverse maternal and fetal outcomes were associated with GDM. Hyperglycemia in pregnancy may cause spontaneous abortion and congenital anomalies in the fetus during early part of gestation, whereas during the middle and later part of gestation, it may lead to excessive fetal weight gain, neonatal hypoglycaemia, jaundice, and stillbirth.[18]

Fetal Outcomes

Fetal macrosomia is one of the most common complications of GDM. Fetal birth weight correlates best with 2nd and 3rd trimester postprandial blood glucose levels. The rate of macrosomia reaches 35% if the postprandial blood glucose levels are more than 160mg/dl.[19-20] Increased maternal blood glucose enters fetal circulation through placenta. Excess glucose is deposited as fat increases the fetal weight.

Increased glucose in fetal circulation stimulates pancreas to secrete insulin leading to fetal hypoglycaemia. Fat deposition occurs mainly in the abdominal and interscapular areas. A macrosomic fetus has decreased head to shoulder ratio,[21] and therefore, Erb's palsy, shoulder dystocia is more common during delivery. In the long term, babies born to GDM mothers are at increased risk of obesity, type 2 diabetes, CVD, and related metabolic diseases. Children of GDM mothers have almost twice the risk of developing childhood obesity compared with non-diabetic mothers, even after accounting for confounding factors such as maternal BMI.[22-23]

Maternal Outcomes

Prolonged labor, perineal tear, uterine atony and postpartum haemorrhage associated with macrosomia necessitates the need for instrumental delivery or lower segmental caesarean section.[24]

In addition to the adverse delivery outcomes due to GDM, there is increased chance of comorbidities during pregnancy such as hypertensive disorders of pregnancy (HDP). About 10 to 30% of women diagnosed with gestational diabetes mellitus are at increased risk for developing HDP.[25] It indicates that gestational hypertension (GH) in GDM patients is caused by vascular dysfunction induced by inflammatory dysregulation which is mediated by adipose tissue and releases proinflammatory and anti-inflammatory factors, including adipokines such as leptin, adiponectin, resistin, and visfatin, as well as cytokines and chemokines such as TNF-α, IL-6, monocyte chemoattractant protein 1 and others. These pro-inflammatory chemicals are actively involved in the development of insulin resistance and the increased risk of cardiovascular disease linked with obesity.[26]

It is well known that GDM is associated with adverse immediate pregnancy outcomes such as gestational hypertension, pre-eclampsia, etc.[27] However, the cardiovascular problem is less during GDM and immediately after GDM. GDM was an independent risk factor for long-term cardiovascular risk.[13,28-29] Pregnant women with GDM have an increased risk of metabolic syndrome, hypertension, insulin resistance dyslipidemia,[30-31] which gradually leads to cardiovascular disease. This is of major concern, as CVD is the number one cause of death in the world.

CARDIOMETABOLIC OUTCOMES IN GDM

GDM and milder signs of prenatal dysglycemia both incline towards dysglycemia shortly after delivery,[32] and 20–30% of women with GDM will suffer from T2DM[33-35] during the first 5 years after delivery,[36] owing to chronic pancreatic beta-cell dysfunction.[37-38] The majority of the dysglycemia was due to the different incidence of postpartum impaired glucose tolerance for GDM.

Dyslipidemia

Dyslipidemia is defined as elevated levels of triglycerides (hypertriglyceridemia) and total blood cholesterol (hypercholesterolemia) including increased low-density lipoprotein (LDL) and reduced high density lipoprotein (HDL) cholesterol. GDM is highly associated with long-term risk of dyslipidemia when compared with their normoglycemic peers. At 3 months postpartum, GDM was found to be independent risk factor of dyslipidemia.[39] Despite the fact that dyslipidemia and T2DM are both risk factors for CVD, and the diagnosis of T2DM is an appropriate justification for dyslipidemia screening, screening women with GDM for dyslipidemia is not a common practice. More than half of women with an abnormal GTT during pregnancy had dyslipidemia when they had a repeat GTT postpartum, according to this prospective research. Dyslipidemia was shown to be prevalent in 78 percent of women with Class II–III obesity.[40] Another study by O'Malley *et al.*[41] assessed the association between GDM and dyslipidemia and concluded that the relationship was mediated through maternal obesity. Obesity during pregnancy might alter the liver's glucose and lipid-lowering metabolism, resulting in hyperglycemia and hyperlipidemia.[42]

Metabolic Syndrome

Women with gestational diabetes mellitus (GDM) are more likely to develop metabolic syndrome (MetS) after delivery. Along with obesity, the prevalence of GDM and MetS has recently increased globally. A study revealed that the risk of MetS was 2.4-fold higher after GDM than after normal pregnancy.[43] According to Di Cianni *et al.*,[31] women with MS had significantly greater levels of insulin resistance, serum uric acid, and CRP following a diabetic pregnancy than women without MetS. Women with a history of GDM who later developed MetS had higher levels of osteoprotegerin (OPG) than those without MetS. Xu Y *et al.*[44] suggested including serum fasting glucose, c-reactive protein, uric acid, and OPG, together with weight and height measures, in the postpartum screening program for GDM women as a forecast of MS.

Hypertension

GDM women with high pre-conception BMI or weight gain > 7Kgs throughout pregnancy increases the risk of development of hypertension in 1 – 5 years after delivery.[45] A prospective cohort study by Tobias DK concluded that women with a history of GDM had a 26% risk of developing hypertension compared to women without history of GDM.[46] Another study by Daly *et al.* concluded that women diagnosed with GDM had 2-fold increased risk of developing hypertension.[3] Hyper-insulinemia, which occurs as a result of insulin resistance, is presumed to mediate increased blood pressure via many mechanisms, including sympathetic nervous system stimulation and reabsorption of sodium from renal tubules.[47]

Type 2 Diabetes Mellitus

Women with GDM have high risk of developing T2DM and the development to T2DM is rapid in the first five years after birth and then

plateaus after ten years. Kim *et al.* reported that the incidence of diabetes after GDM ranges between 2.6 to 70% in women evaluated from 6 weeks to 28 years postpartum.[36] Another study by Bellamy *et al.* reported 7-fold higher risk of development of T2DM in women with history of GDM when compared to normal pregnant women.[48]

Cardiovascular Disease

GDM is associated with an increased risk of CVD 10 years after delivery.[49] McKenzie-Sampson *et al.* reported GDM was associated with increased risk of ischemic heart disease and myocardial infarction.[50] Kramer *et al.* conducted a systematic review and meta-analysis to ascertain whether CVD risk is dependent upon the intercurrent development of T2DM.[51] Women with GDM had 2-fold increased risk of CVD in future and the association remained even after restricting to women who did not develop T2DM.

GDM triggers the development of atherosclerosis by endothelial dysfunction. Women with GDM had higher carotid artery intima thickness and impaired flow mediated dilatation of the brachial artery compared to pregnant women without GDM which suggests the development of atherosclerosis in pregnant women with GDM.[52-56]

PATHOPHYSIOLOGY OF CARDIOMETABOLIC RISKS IN GDM

The pathophysiological mechanisms of cardiovascular risk in GDM is multifactorial (Figure 1). Insulin resistance in GDM causes dyslipidemia. Dyslipidemia along with endothelial dysfunction causes atherosclerotic plaque eventually leading to cardiovascular disease.[57]

Subclinical inflammation, which appears to be prevalent in GDM and predictive of higher cardiovascular events in the female population, is mediated in part by the paracrine action of adipocytes.[58-59] Low adiponectin concentrations early in pregnancy are linked to an increased chance of having GDM because adiponectin expression is reduced in obesity, insulin resistance, and T2DM.[60-62] Compared to control subjects, women with prior GDM had significantly higher levels of C-reactive protein, interleukin-6, and plasminogen activator 1 and lower levels of adiponectin. However, after controlling for confounders, only elevated levels of C-reactive protein and low levels of adiponectin were linked to GDM. In addition to T2DM, women whose pregnancies were worsened by GDM have also been reported to experience microalbuminuria, a marker of compromised endothelial function. The researchers suggested that maternal vascular endothelial dysfunction may raise the risk of cardiovascular diseases in women who had had gestational diabetes in the past.[58]

Endothelial dysfunction is known to be an early sign of atherosclerosis.[63] Maximal endothelium-dependent dilation (EDD) of arteries from GDM-affected women (43.3%) and from those with milder gestational dysglycemia (51.7%) was substantially lower than it was for normoglycemic controls (72.7%).[64-65] EDD, which indicates nitric oxide (NO) synthesis and NP bioavailability, is assessed by flow-mediated dilation (FMD).[66] Established CVD as well as several conventional cardiovascular risk variables are linked to an attenuated FMD response, which is currently thought to be predictive of elevated cardiovascular risk. Paradisi *et al.*[67] reported lower FMD response in the third trimester of pregnancy in GDM women and in pregnant women with mild forms of dysglycemia. At 2 months postpartum, FMD was impaired in both normoglycemic women who had prior GDM and those who remained hyperglycemic.[53] Another study by Anastasiou *et al.*[68] studied FMD response in obese and non-obese women who had prior GDM and restored normoglycemia at 3 to 7 months postpartum. FMD was significantly decreased in both obese and non-obese GDM women compared to control in which the arterial dilation is proposed due to endothelial and smooth muscle dysfunction. Lekakis JP *et al.*[69] proposed that generation of oxygen-derived free radicals impaired endothelial responsiveness from the report that FMD was significantly increased following administration of ascorbic acid. In contrast, another study reported no significant difference in FMD response at 5 years postpartum suggesting the EDD detected in early postpartum is reversible.[70] However, those with prior GDM showed evidence of microvascular dysfunction, which could be due to altered microvascular vasoreactivity caused by decreased NO bioavailability. These findings were supported by Mittermayer F *et al.*[71] who reported increased NO synthase inhibitor ^{N}G-dimethyl-L-arginine in GDM women.

In diabetes, calcineurin/NFAT signaling pathway gets activated due to amylin aggregation in heart leading to cardiac hypertrophy and causes cardiovascular risk.[72] In GDM, there occurs oxidative stress,

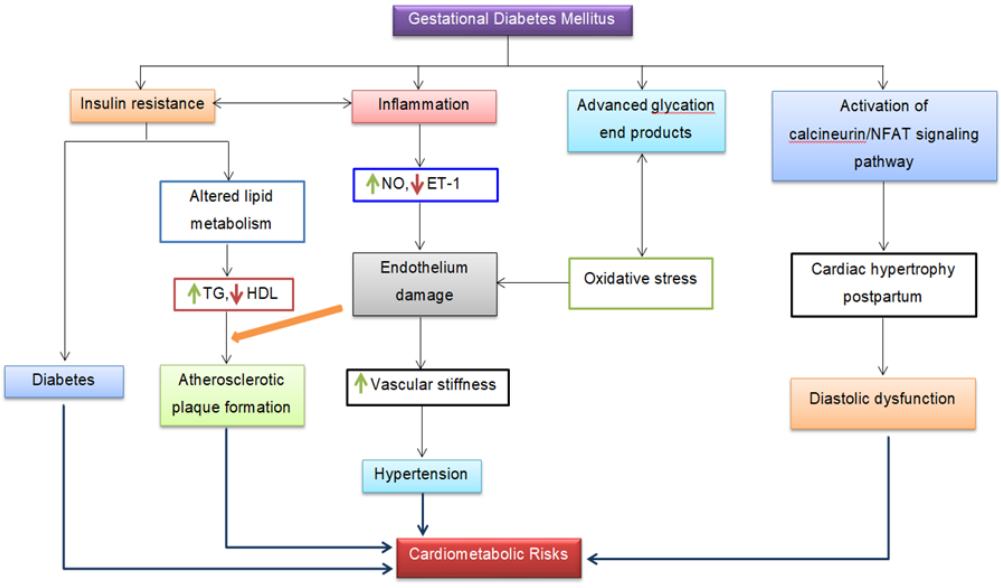

Figure 1: Pathophysiology of cardiometabolic risks in gestational diabetes mellitus.

inflammation and endothelial damage causing vascular stiffness leading to cardiovascular risks.

Though pregnant women with GDM are at higher risk of immediate and long-term adverse effects such as dyslipidemia, type 2 diabetes, cardiovascular disease, insulin resistance, hypertension, etc., all these cardiovascular risks can be reduced by lifestyle modification and adherence to management. Lifestyle modifications such as diet, physical activity, yoga, pranayama, etc. can be followed to reduce the cardiovascular risks.

CONCLUSION

The incidence of GDM is increasing in recent times. Women with GDM have risk of development of cardiometabolic risk in future in addition to poor fetal, maternal and neonatal outcomes during and after delivery. Both GDM and cardiovascular disease share common etiopathogenesis such as inflammation, endothelial dysfunctions and oxidative stress, which can be reduced by lifestyle modifications.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GDM: Gestational Diabetes Mellitus; **T2DM:** Type 2 Diabetes Mellitus; **CVD:** Cardiovascular Disease; **CMR:** Cardiometabolic Risks; **HDP:** Hypertensive Disorders of Pregnancy; **GH:** Gestational Hypertension; **MetS:** Metabolic Syndrome; **OPG:** Osteoprotegerin; **EDD:** Endothelium-Dependent Dilation; **NO:** Nitric Oxide; **FMD:** Flow-Mediated Dilation.

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