

# Risk of Cardiovascular Diseases in Women with Gestational Diabetes

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DOI: <https://doi.org/10.52403/ijhsr.20231226>

## ABSTRACT

Gestational diabetes mellitus (GDM), a condition characterized by glucose intolerance during pregnancy, has been associated with a range of pregnancy related complications and long-term health risks. This review focuses on the emerging evidence connecting GDM to an increased risk of cardiovascular diseases (CVD) in women. While the link between GDM and the subsequent development of type 2 diabetes has been well established, recent studies have also revealed a heightened risk of CVD in women with a history of GDM. The increased risk of CVD appears independent of concurrent type 2 diabetes onset. Various factors, including insulin resistance, obesity, genetic predisposition, and placental hormone effects, contribute to the complex pathophysiology underlying the connection between GDM and CVD. This review discusses the epidemiology, aetiology, and pathophysiology of CVD risk in women with GDM, emphasizing changes in circulatory system, markers for CVD, and potential diagnostic indicators. Management strategies encompass lifestyle modifications, medications, blood sugar monitoring and postpartum monitoring. The review concludes by highlighting the importance of early identification and intervention of cardiovascular risk factors in women with a history of GDM, and the necessity for further research into preventive measures and targeted interventions to mitigate the long-term cardiovascular impact of GDM.

**KEYWORDS:** Gestational diabetes mellitus, cardiovascular diseases, pregnancy, hyperglycaemia, insulin, blood sugar.

## INTRODUCTION

Glucose intolerance that develops during pregnancy is known as gestational diabetes mellitus (GDM) [1]. Short-term pregnancy problems such preeclampsia, preterm birth, stillbirth, macrosomia, and caesarean birth are linked to GDM [2,3]. Although GDM typically goes away after childbirth, its effects go beyond pregnancy [1]. According to studies, women who have experienced GDM are more likely to eventually acquire type 2 diabetes, the metabolic syndrome, chronic renal disease, and cardiovascular disease (CVD) [4]

While glucose tolerance usually returns to normal in the first few days following delivery, women with GDM have a 20–70% chance of developing type 2 diabetes within the first decade [5]. Given that affected women have an overall incidence of type 2 diabetes that is more than seven times higher than that of their counterparts, GDM is an established clinical indicator of future diabetes risk.

Although the link between pregnancy-related hyperglycaemia and type 2 diabetes has been known for more than 50 years, the link between cardiovascular disease (CVD)

and CVD has only recently come to light. Notably, a number of studies conducted recently have revealed that women with GDM experience a higher risk of significant cardiovascular events in the years to decades postpartum, while being relatively young (i.e., of childbearing age) [6]. 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. For example, some studies have claimed that women with GDM only acquire cardiovascular disease (CVD) if they proceed to type 2 diabetes [6,7,8]

The associations between a history of GD, glucose tolerance later in life, and cardiovascular risk as measured by coronary artery calcium (CAC) in women participating in the CARDIA project (Coronary Artery Risk Development in Young Adults).<sup>7</sup> Women with a history of GD were shown to have an elevated risk of CAC, which was found to be unrelated to many other clinical, lifestyle, and social risk factors. This finding supports the idea that GD itself increases the risk of future cardiovascular events.[<sup>9</sup>]

### **EPIDEMIOLOGY:**

When the maternal insulin secretion is insufficient to meet the increased insulin demand during pregnancy, gestational diabetes mellitus (GDM) develops.<sup>10</sup> Depending on screening methods, diagnostic standards, and population variables, the prevalence of GDM varies from 1% to 30% globally [11]. The incidence is 3% in Denmark. Obstetric problems such as hypertensive disorders, caesarean sections, and premature birth are more likely to occur in women with GDM [11]. Women are more likely than males to have an increase in relative risk of vascular disease linked with a T2D diagnosis, and this risk is thought to be unrelated to other conventional cardiovascular risk factors.[12]

### **ETIOLOGY:**

The relation between GDM and cardiovascular diseases may have some modifiable and unmodifiable risk factors such as insulin resistance, dyslipidaemia, obesity, metabolic syndrome, genetic and epigenetic factors, type 2 diabetes, lifestyle, inflammation, hypersensitivity disorders, endothelial dysfunction etc.[13]

Risk in women may be partially attributed to the larger weight increase needed for them to acquire T2D or to the longer time they spend in the metabolically unfavourable stage of prediabetes compared to males who develop T2D.[14] The CARDIA results confirm GD as another separate diabetes-related risk factor for women's cardiovascular health. This risk may be linked to the actions of placental hormones or to the increased production of inflammatory cytokines during pregnancy, both of which enhance insulin resistance and may encourage atherogenesis. [14,15] A high-risk vascular phenotype, however, may exist in some women prior to conception but may not be discovered until routine GD screening.[15]

The CARDIA results prevent us from drawing this difference, and it is also impossible to determine the effects of the degree of hyperglycaemia, glycaemic control techniques, or concurrent risk factors like hypertension during pregnancy. The CARDIA results support the idea that GD is a new risk factor for ischemic coronary heart disease in women, though.[17]

Increased risks of coronary artery disorders, heart attacks (myocardial infarction), heart failure, angina, cardiovascular operations, and stroke were observed in women with gestational diabetes. Women with a history of gestational diabetes were also shown to have a 28% increased chance of developing life-threatening blood clots (venous thromboembolism).

Pregnant women may experience cardiovascular and metabolic difficulties as a result of physiological changes during pregnancy, such as increased circulatory

volume, inflammatory alterations, insulin resistance, and hyperlipidaemia. Pregnancy complications like gestational diabetes, preeclampsia, preterm delivery, and small or large for gestational age can arise as a result of these changes, and it has been reported that women who experience pregnancy complications are more likely to go on to develop cardiovascular disease after giving birth [18,19,20].

### **PATHOPHYSIOLOGY: CHANGES IN THE CIRCULATORY SYSTEM IN WOMEN WITH HISTORY OF GESTATIONAL DIABETES MELLITUS**

The onset of atherosclerosis appears to be sped up by GDM, which appears to have a major effect on endothelial shape and function. Heart disease and stroke are substantially predicted by carotid artery intima-media thickness (cIMT), a subclinical indicator of early atherosclerosis, especially in females [21]. After correcting for waist size, BMI, blood pressure, and blood glucose levels, a multiple regression analysis revealed that cIMT was also substantially linked with a history of GDM. 28 women with and 24 without a history of GDM participated in Volpe et al.'s study of cIMT two years after delivery [22]. Regarding BMI, there were no differences between the two groups, however the GDM women's cIMT readings were higher even though they were still within the normal range. The author came to the conclusion that a history of GDM could be viewed as a risk factor for atherosclerosis even in the absence of diabetes or the metabolic syndrome.

The flow-mediated dilation (FMD) of the brachial artery, which is a hallmark of endothelial dysfunction and one of the first symptoms of atherosclerosis [23], has also been suggested as a surrogate marker for the early diagnosis of atherosclerosis. In a recent study, Caliskan et al. looked at the coronary flow velocity reserve (CFVR), which represents the function of the coronary microvasculature, in postpartum

women with a history of GDM. They also discovered that insulin resistance, hyperglycaemia, and oxidative stress indicators were inversely linked with CVFR. They found that this parameter was considerably lower in GDM women than in controls whose glucose tolerance was unaffected during pregnancy.[24]

### **MARKERS FOR CVD IN WOMEN WITH GDM:**

When a woman is pregnant, the placenta is the main organ that expresses placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1). Proangiogenic PlGF uses the antiangiogenic sFlt-1 as a sham receptor [28]. As a result, the pregnancy-related angiogenic profile can be determined by the relative circulating amounts of sFlt-1 and PlGF. This ratio may be a marker for future cardiovascular risk in GDM women.

A number of molecular biomarkers, including growth-differentiation factor 15 (GDF-15) [19], circulating cardiac troponin T (cTnT) [25], and N-terminal pro-B-type natriuretic peptide (NT-proBNP) [26], are useful in the detection of preclinical heart disease. cTnT is associated with markers of oxidative stress, arterial pulse wave reflection, and advanced glycation end-products (AGE) [27], and it may be used as a biomarker for patients with diabetes who have an elevated risk of coronary artery disease. In patients with DM1 [29] and DM2, NT-proBNP may function as an independent risk factor for CVD. The glycocalyx has been shown to sustain significant damage from hyperglycaemia. The destruction of this barrier proteoglycan layer has been linked to microvascular illness in capillaries and arterioles, as well as atherosclerosis in larger arteries [30].

### **DIAGNOSIS:**

The following two tests are used for the diagnosis of gestational diabetes in pregnant women:

### **INITIAL GLUCOSE CHALLENGE TEST**

You will consume a syrupy glucose solution. You'll undergo a blood test to check your blood sugar level one hour later. Pregnancy-related diabetes is identified by a blood sugar level of 190 mg/dL, or 10.6 mmol/L.

On a glucose challenge test, a blood sugar level below 140 mg/dL (7.8 mmol/L) is typically regarded as being within the normal range, though this can vary by clinic or lab. You will require a second glucose tolerance test to determine if you have gestational diabetes if your blood sugar level is greater than expected. [31,32]

### **FOLLOWUP GLUCOSE TOLERANCE TEST**

This test is identical to the first one, except your blood sugar will be monitored hourly for three hours and there will be more sugar in the glucose solution. Gestational diabetes will be identified if at least two of the blood sugar values are higher than normal. [29,30]

### **MANAGEMENT:**

#### **LIFESTYLE MODIFICATIONS**

Lifestyle, the food we take, exercise all are a crucial part of keeping the blood sugar levels in a healthy range. Losing weight during pregnancy is not recommended during pregnancy as the body is already working hard to support the growth of baby. The weight goals can be set by healthcare provider based on the weight before pregnancy.[34]

#### **HEALTHY DIET:**

Taking foods like green vegetables, lean protein, fruits, foods rich in fibre, dry fruits, whole grains, food with less fat should be taken. Foods like carbohydrates, sweets, carbonated drinks, caffeine should be avoided. The healthcare providers can suggest a diet plan based on the weight and the blood sugar levels.[34]

### **EXERCISE:**

Regular activity can keep the body fit before, during and also after the pregnancy. It helps keep the blood sugar levels in control. Exercise also helps relieve the pregnancy symptoms like body pains, constipation, sleeping problems, back pain etc. At least 30 minutes of exercise a day is important. Walking is a best option during pregnancy which can help them stay active.[33]

### **MEDICATIONS:**

Your blood sugar levels may need to be lowered with insulin injections if diet and exercise are insufficient to control them. Some pregnant women with gestational diabetes require insulin to achieve their blood sugar targets. To control blood sugar levels, some healthcare practitioners recommend an oral medicine. The management of gestational diabetes, in the opinion of other medical professionals, requires more investigation to determine whether orally administered drugs are equally secure and efficient to injectable insulin.[35]

### **MONITORING OF BLOOD SUGAR:**

In order to ensure that your blood sugar level remains within a healthy range while you are pregnant, your medical team may advise you to check it four or more times per day, preferably first thing in the morning and after meals.[35]

### **MONITORING FOLLOWING DELIVERY:**

After birth and again six to twelve weeks later, your doctor will check your blood sugar level to be sure it has returned to the normal range. You must have your diabetes risk evaluated at least every three years if your tests fall back into this range, as they almost always do.

Talk to your doctor about stepping up your preventative efforts or establishing a diabetes management plan if further tests reveal type 2 diabetes or prediabetes.[32]

## DISCUSSION

Gestational diabetes is a type of diabetes that appears during pregnancy when sugar levels are very high. It usually appears during mid pregnancy that is between 24 to 28 weeks. The following studies have shown an association between the risk of cardiovascular diseases due to gestational diabetes. Few review articles were referred and the following results were observed regarding the risk of cardiovascular diseases in women with gestational diabetes.

In this population-based cohort study, 10,02,486 Danish women who had given birth between 1978 and 2016 were included. Using full-cohort and sibling-matched analyses, we used Cox regression to 1) examine the relationships between GDM and general and type-specific CVDs, 2) calculate the impact of type 2 diabetes after GDM, using mediation analysis, and 3) determine whether these relationships were affected by pre pregnancy obesity or maternal history of CVD and it was concluded that the risk of both general and specific CVDs was shown to be higher in people with a history of GDM. Subsequent type 2 diabetes contributed to the explanation of increased risks, but other routes still need to be found. Continuous monitoring of women with a history of GDM, particularly those who are obese prior to conception or have a mother who has had a cardiovascular disease, may offer better opportunity to lower their cardiovascular risk.[36]

Data from 5,390,591 women (101,424 cardiovascular incidents) were collected through the pooled analysis of nine trials. Women with GDM exhibited a twofold greater risk of future cardiovascular events compared to those without GDM (RR 1.98 [95% CI 1.57, 2.50]). The incidence rates of type 2 diabetes across the studies did not change this risk, according to a meta-regression analysis ( $p = 0.34$ ). Additionally, GDM was still linked to a 56% greater risk of future cardiovascular events when limited to women who did not develop type 2 diabetes (RR 1.56 [95% CI 1.04, 2.32]). In

the first decade postpartum, GDM was associated with a 2.3-fold increased risk of cardiovascular events (RR 2.31 [95% CI 1.57, 3.39]) and concluded that young women with GDM are two times more likely than their peers to experience cardiovascular problems after giving birth. This risk manifests within the first decade following conception and is independent of concurrent type 2 diabetes. Women with GDM are therefore at-risk for CVD even if they don't develop type 2 diabetes, providing a possible opportunity for early risk factor surveillance and risk management.[37]

Data were gathered from 12,025 women (20 years) who participated in the National Health and Nutrition Examination Survey, 2007–2018 and had at least one live delivery. The multivariable-adjusted risk ratios (95% confidence intervals) for CHD, heart failure, and stroke among women with a history of GDM were 1.82 (1.21-2.72), 1.43 (0.80-2.53), and 1.19 (0.76-1.86), respectively, compared to women without GDM. The extra odds of CHD, heart failure, and stroke linked with GDM were each associated with type 2 diabetes at a rate of 43.90, 67.44, and 63.16%, respectively. The odds ratios (with 95% confidence intervals) for CHD (12 studies, 7,615,322 participants,  $I^2 = 72.6\%$ ), heart failure (5 studies, 4,491,665 participants,  $I^2 = 88.6\%$ ), and cerebrovascular disease (9 studies, 6,090,848 participants,  $I^2 = 77.8\%$ ) were 1.81 (1.60–2.05), 1.66 (1.25-2.21), and 1.25 (1.07–1.46), respectively and concluded that Compared to cerebrovascular disease, GDM revealed greater links with coronary heart disease and heart failure, and the increased risks are partially attributed to type 2 diabetes.[38]

The analysis comprised 1,500,168 parous women in total, of whom 159,066 (10.60%) had GDM. 13,222 incident cases of all CVD were reported during a median follow-up of 12.8 years. those with a history of GDM had a multivariable-adjusted hazard ratio for total CVD of 1.08 (95% CI: 1.01-1.14), compared to those without a history of

GDM. GDM was further categorized by progression to T2DM in relation to overall CVD risk, and this revealed a positive correlation for GDM with advancement to T2DM compared to no GDM or T2DM (HR 1.74; 95% CI 1.40-2.15), but no statistically significant connection for GDM alone (HR 1.06; 95% CI 1.00-1.12). Cardiovascular illnesses were connected to an increased incidence of GDM with eventual development to T2DM. These results demonstrate the necessity of more thorough postpartum screening for diabetes and application of diabetic therapies in women with a history of GDM to lower risk of future CVD.[39]

## CONCLUSION

In summary, multiple studies have shown that women who acquire GDM have an increased risk of CVD and type 2 diabetes following delivery, however the mechanisms causing the vascular dysfunction seen in GDM women are still unknown. Future research should focus on finding reliable early indicators of CVD in women who develop GDM, and targeted approaches are needed to prevent or lower obesity, diabetes, metabolic syndrome, and subsequent CVD in this particular population. The beginning of cardiovascular events in women with a history of GDM is partially explained by chronic metabolic comorbidities such diabetes, hypertension, and dyslipidemia. For women with a history of GDM, it is indicated that routine screening and long-term appropriate interventions for CVD prevention are required.

### *Declaration by Authors*

**Ethical Approval:** Not Required

**Acknowledgement:** None

**Source of Funding:** None

**Conflict of Interest:** The authors declare no conflict of interest.

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How to cite this article: Karra, Geetha, R. Sakshi, T. Chandana, Ch. Sai Chandu, T. Rama Rao. Risk of cardiovascular diseases in women with gestational diabetes. *Int J Health Sci Res*. 2023; 13(12):215-222.  
DOI: <https://doi.org/10.52403/ijhsr.20231226>

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