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# Late Cardiovascular Consequences of Gestational Diabetes Mellitus

**Rhonda Bentley-Lewis, M.D., M.B.A., M.M.Sc.**[1,2]

[1]Instructor in Medicine, Harvard Medical School, Boston, Massachusetts.

[2]Associate Physician, Division of Endocrinology, Diabetes, and Hypertension, Department of Medicine, Brigham and Women's Hospital, Boston, Massachuserts.

## Abstract

Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance of any degree first recognized during pregnancy, complicates ~4% of all pregnancies in the United States. Several factors can increase one's risk of developing GDM, including obesity, family history of type 2 diabetes mellitus (T2DM), and race/ethnicity. Conversely, a history of GDM can increase the risk of developing not only T2DM but also cardiovascular disease (CVD) independent of a diagnosis of T2DM. Several investigations have explored GDM relationships with CVD risk factors, CVD surrogate markers, and clinically evident CVD. These studies have included evaluations of biochemical parameters, such as inflammatory and endothelial biomarkers; endothelial dysfunction, such as that seen in impaired brachial artery flow-mediated vasodilation; and vascular dysfunction, manifest as cardiac dysfunction or in diseases such as hypertension. This article will review these studies and examine factors considered to be responsible for promoting CVD in women with a history of GDM, such as T2DM and metabolic syndrome and its components. In addition, studies evidencing CVD in women with a history of GDM will be explored.

### Keywords

Gestational diabetes mellitus; cardiovascular disease; endothelial dysfunction; inflammation; biomarkers

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Gestational diabetes mellitus (GDM), defined as carbohydrate intolerance of any degree first recognized during pregnancy, [1] complicates ~4% of all pregnancies in the United States with a prevalence of 1 to 14% and an annual incidence of more than 135,000 cases.[1] Prevalence estimates of GDM vary depending on the population under examination, and several studies report that the prevalence of GDM is higher among racial/ethnic minorities compared with that among non-Hispanic white populations.[2-5] One population study reported that the age-adjusted prevalence of GDM per 100 births in 2005 was 4.9% among non-Hispanic whites and 5.2% among non-Hispanic blacks.[4] Additionally, the increasing



Address for correspondence and reprint requests; Rhonda Bentley-Lewis M.D., M.B.A., M.M.Sc., Associate Physician, Brigham and Women's Hospital, Department of Medicine, Division of Endocrinology, Diabetes, and Hypertension, 221 Longwood Avenue, Boston, MA 02115 (rbentleylewis@partners.org)..

prevalence among ethnic minorities of risk factors associated with the development of GDM, such as obesity[6] suggests that the racial disparity in GDM prevalence will persist.

There are several factors that can increase the risk of developing GDM, including obesity,[7] family history of type 2 diabetes mellitus (T2DM),[8] and race/ethnicity.[8] Notably, features that increase the risk of developing GDM, including obesity and the metabolic syndrome components, are also associated with an increased risk of developing cardiovascular disease (CVD).[9] Normoglycemic pregnancy presents a metabolic stress characterized by insulin resistance with postprandial hyperglycemia; dyslipidemia with increased triglycerides and low-density lipoprotein (LDL); and increased inflammation including elevated C-reactive protein (CRP) and plasminogen activator inhibitor-1 (PAl-1).[10] Therefore, the stress imposed by GDM on an already compromised metabolic state can potentially convert a usually transient metabolic derangement into a more permanent abnormality that will increase the likelihood ofCVD development. This review will examine investigations of GDM with respect to CVD risk factors, such as T2DM; CVD surrogate measures, such as endothelial dysfunction; and diagnosed CVD, such as coronary artery disease (Table 1).

## CARDIOVASCULAR DISEASE RISK FACTORS

### Type 2 Diabetes Mellitus

Type 2 diabetes mellitus has been considered a CVD risk equivalent,[11] and it is well established that GDM increases the risk for the development of T2DM.[12] Di Cianni et al[13] showed that women who underwent an oral glucose tolerance test (OGTT) 2 years after a GDM pregnancy, then classified as having diabetes, impaired glucose tolerance (IGT), or normal glucose tolerance, demonstrated significantly impaired insulin sensitivity and increased insulin resistance compared with women with prior normal pregnancy. Several investigations have shown that women with a history of GDM have a 17 to 63% risk of developing T2DM within the *5* to 16 years after the GDM pregnancy.[14,15] Studies have also demonstrated that the rate of conversion from GDM to postpartum T2DM differs based on characteristics such as the ethnicity of the women and insulin use during pregnancy.[16]

### Blood Pressure

High blood pressure is a well-established modifiable risk factor for coronary heart disease.[17] High blood pressure during pregnancy, as seen in gestational hyper-tension[18] or preeclampsia,[19] has been associated with insulin resistance. In fact, women with higher glucose and insulin levels are more likely to develop preeclampsia,[20] and women with a history of preeclampsia have greater insulin resistance[21] and an increased incidence of hypertension when studied several years after delivery.[22] Additionally, one study of women 2 to *5* years after a pregnancy complicated by GDM found that these women had higher systolic blood pressures than that of women With normoglycemic pregnancies.[23] Moreover, beyond the relationships among hyperglycemia, hyperinsulinemia, and hypertension, a diagnosis of G DM has also been associated with increased blood pressure.[10]

Bryson et al[24] examined the relationship between GDM and hypertension by conducting a case-control analysis of birth records of mothers delivering infants in Washington state between 1992 and 1998. Diagnoses of pregnancy-induced hypertension (PIH) were

identified by International Classification of Diseases, Ninth Revision (ICD-9), codes and divided into populations with gestational hypertension ($n$ = 8943), mild preeclampsia ($n$ = 5468), severe preeclampsia ($n$ = 1180), and eclampsia ($n$ = 154). Gestational diabetes was also identified by ICD-9 code, and a control population ($n$ = 47, 237) was selected by random sampling. The women with PIH were younger, had lower body mass index (BMI), were more often primigravid, and had more prenatal care compared with those of the control women. The data revealed that, after adjusting for BMI, age, race/ethnicity, parity, and adequate prenatal care, GDM was significantly associated with mild and severe preeclampsia as well as gestational hypertension with odds ratios (ORs) of 1.50, 1.53, and 1.40, respectively. Of note, after the same statistical adjustments previously noted, white mothers with gestational diabetes had a 1.3 to 1.5 greater risk of falling into one of the PIH categories, whereas black mothers had a 3- to 4-fold greater risk of PIH compared with that of their racially matched controls. Although this study is limited by its use of administrative data to derive its populations, a Swedish study using similar methods also found a significantly increased risk of preeclampsia (OR, 3.16; 95% CI [1.65, 6.03]) and insignificantly increased risk of gestational hypertension (OR, 1.34; 95% CI [0.49, 3.71]) among women with GDM.[25]

A study using actual measurements of blood pressure has also examined the link between GDM and blood pressure. Noninvasive ambulatory arterial pressure monitoring (AAPM) has been performed reliably during pregnancy and found to be highly correlated with end-organ damage and left ventricular hypertrophy.[26] Oren et al[27] performed AAPM on women in the third trimester of pregnancy who were normotensive, hypertensive, or had GDM. There were 10 women in each group at similar gestational ages, but the GDM women were significantly older and slightly more over-weight than the women of other two groups. All of the women maintained a normal reduction in mean arterial pressure during the night; however, the decrease in blood pressure was less in the GDM group than that in the normotensive group (8 mm Hg vs. 12 mm Hg; $p$ = NS) and the heart rate of the GDM women was significantly greater than that of the other two groups (75 ± 6.4 vs. 64 ± 2.6; $p < 0.001$).

## Lipid Profile

An uncomplicated pregnancy is notable for a lipid profile that promotes CVD risk, characterized by increased triglycerides and small, dense LDL particles.[28] In addition, glucose intolerance, either T2DM or GDM, augments the atherogenicity of the lipid profile. In women with a history of GDM, there is a significant difference in postpartum fasting lipid levels in these women compared with those of women who had normoglycemic pregnancies.[29] Meyers-Seifer and Vohr studied 56 women after a pregnancy complicated by GDM and 48 women after a normoglycemic pregnancy.[29] These women were all within *5* to 6 years postpartum and underwent metabolic, anthropometric, and hemodynamic assessments. The two groups did not differ based on age, BMI, or socioeconomic status; however, more women with GDM had a family history of T2DM compared with that of the controls (40% vs. 15%; $p$ = 0.008). Total cholesterol, triglyceride, and LDL-cholesterollevels were significantly higher in the women with GDM compared with that in the controls, whereas the high-density lipoprotein (HDL)-cholesterol did not differ between

the two groups. In addition, systolic blood pressure was also higher among the women with a history of GDM. In fact, elevated triglyceride levels correlated with BMI, insulin, and systolic blood pressure p;1ramctcrs, whereas HDL-cholesterol correlated inversely with insulin levels in the GDM women only, evidencing a clustering of these metabolic abnormalities in the GDM population similar to that seen m the metabolic syndrome.

### Metabolic Syndrome

Metabolic syndrome has been observed to be more prevalent among women with a history of GDM than among women without GDM.[30,31] A study of young, obese, premenopausal women revealed that those with a history of GDM were more likely to have the metabolic syndrome than were those without a GDM history (86.6% vs. 73.5%; $p < 0.001$).[32] This increased prevalence has been attributed to various causes, including an increased frequency of abdominal obesity and lower HDL levels, or to GDM unmasking prepregnancy metabolic syndrome.[33]

Data from an examination of the National Health and Nutrition Examination Survey III revealed that women with a history of GDM ($n = 85$) had similar cardiovascular risk factor profiles, including blood pressure and lipid parameters, compared with that of women with a pregnancy history free of diabetes ($n = 4328$).[34] However, the absolute number of metabolic syndrome characteristics was indeed greater among women with a history of GDM compared with that among the unaffected women. Additionally, this population of women with a history of GDM was relatively small, and the authors note that it may have represented a relatively healthier population of women compared with the women with GDM histories who developed T2DM who were not included in the study.

## CARDIOVASCULAR DISEASE SURROGATE MEASURES

### Endothelial Dysfunction

The endothelium, the largest endocrine organ,[35] secretes vasoactive substances, such as vasodilators like nitric oxide and vasoconstrictors like angiotensin, that exert counterbalancing forces on the vasculature.[36,37] VasCular disease represents an imbalance in these forces leading to increased vasoconstriction, inflammation, and, ultimately, impaired endothelial function. Risk factors for CVD, such as smoking, obesity, hypertension, and diabetes, impair endothelial function.[36,38,38,39] The severity of endothelial dysfunction has been associated with the risk for an initial or recurrent cardiovascular event,[40–43] and medical and lifestyle interventions that reduce CVD risk have been associated with improved endothelial function.[44,45] Therefore, identifYing endothelial dysfunction would be valuable because this represents preclinical CVD that could benefit from primary prevention efforts.

Assessment of endothelial function reflected in nitric oxide synthesis derangements has been evaluated both during and after pregnancy complicated by GDM. During pregnancy, an investigation of brachial artery flow-mediated dilation (FMD), a technique strongly correlated with the invasive assessment of endothelial function in coronary arteries,[46] was performed in a population of pregnant women grouped as 15 normoglycemic, 10 IGT, and

13 GDM. This study revealed that the women with IGT had FMD at 70% of the control group's FMD, and the GDM groups' FMD was only 38% that of the controls.[47]

After delivery, vascular dysfunction has been examined in women with a history of GDM. One Swedish study revealed increased common carotid artery stiffness and impaired extremity acetylcholine-induced vasodilation in 17 women 2 to 4 years after GDM delivery compared with that in 20 women with normal pregnancy histories.[48] Another study observed impaired FMD among women with a history of GDM, and significantly decreased nitrate-induced dilation in the obese post-GDM women, compared with that in women after normal pregnancies studied 3 to 6 months after delivery and segregated by BMI <27 ($n$ = 17) and BMI ≥.27 ($n$ = 16).[45]

Another measure of vascular function is carotid intimal-medial thickness (CIMT). CIMT has been known to be a marker of preclinical atherosclerosis[49] and is commonly used as a surrogate of vascular disease morbidity and mortality.[50] CIMT has also been shown to be predictive of CVD in T2DM[51] and found to regress in cases of improved glycemia in T2DM.[52] Tarim et al[53] studied 30 women with GDM and 40 normoglycemic women of similar age and BMI in the second trimester of pregnancy. They observed that CIMT was significantly greater among the women with GDM compared with that among the non-GDM women (0.582 ± 0.066 *mm vs. 0.543 ± 0.049 rom; $p$ = 0.006); however, no studies were performed post-partum to determine if these differences resolved with resolution of the GDM.

Another study of CIMT in women with a history of GDM involved 28 women with and 24 women without a history of GDM 2 years after delivery.[23] The women with a history of GDM were significantly older, had higher blood pressure (although still within normal range) and waist circumference (although similar BMis) compared with that of the women with normoglycemic pregnancy histories. Although the postpartum OGTI revealed that nine of the women post-GDM had impaired glucose tolerance and/ or impaired fasting glucose, none had diabetes. The mean common CIMT was greater among the women with prior GDM compared with that of controls (0.57 ± 0.058 mm vs. 0.51 ± 0.051 mm; $p$ < 0.01).

Two additional investigations of CIMT were performed by Xiang in the setting of a thiazolidinedione intervention. The Troglitazone in the Prevention of Diabetes (TRJPOD) study examined the use of troglitazone or placebo in obese Hispanic women with a previous history of GDM.[54] Among the women who had follow-up CIMT measured, there were no baseline differences between those who received troglitazonc ($n$ = 93) and 'those who received placebo ($n$ = 99), including BMI, blood pressure, lipids, and glucose tolerance. However, the authors observed that the average rate of change of CIMT was 31% lower in the troglita-zone group ($6.5 \times 10\text{-}^{3}$ mrnly) that than that in the placebo group ($9.4 \times 10\text{-}^{3}$ *mmly; p*=0.05). Of note, there was also a 55% risk reduction in progression to T2DM in women who received troglitazone when compared with that of those who received placebo.

The Pioglitazone in Prevention of Diabetes (PIPOD) study[55] enrolled women who had completed TRJPOD without developing T2DM. These women were randomly assigned to receive either pioglitazone or placebo for a period of 3 years; there were 31 women who

entered the study after troglitazone and 30 women who had received placebo. Mter treatment with pioglitazone, the CIMT progression rate was 69% lower in the women who had initially received placebo (0.0031 mm/y vs. 0.010 *mmly; p* = 0.006) and 38% lower in the women who had received troglitazone (0.0037 *mmly* vs. 0.0060 *mmly; p*=0.26). Of note, a 4.6% yearly incidence rate of T2DM was reported in the pioglitawne group compared with 12.1% in the placebo group.

## Biochemical Markers

Several biochemical parameters have been examined with respect to GDM, including asymmetric dimethylargimne[56,57] and measurements of nitric oxide production. [58] Insulin resistance is also associated with endothelial dysfunction through alterations in nitric oxide. Insulin stimulation of nitric oxide production via increased nitric oxide synthase activity is associated with increased endothelium-dependent vasodilation in healthy individuals. However, in those who manifest insulin resistance, this nitric oxide--mediated vasodilation is decreased.[59] Pharmacologic interventions that improve insulin resistance have also been shown to improve endothelium-dependent vasodilation.[60,61] Additionally, insulin resistance is associated with increased levels of free fatty acids, which can in turn decrease nitric oxide synthase activity and reduce nitric oxide production in insulin resistance.[62]

Biochemical markers of endothelial dysfunction have also been investigated in GDM populations. A small population study by Kautzky-Willer et al demonstrated that E-selectin and vascular adhesion molecule-1 (VCAM-1) were elevated in women after a GDM pregnancy compared with that in women after a normal pregnancy, whereas intercellular adhesion molecule-1 (ICAM-1) did not differ between the two groups.[63] A larger study found elevations in ICAM-1 and E-selectin in the women studied within 6.5 years after GDM pregnancy, but observed no differences in VCAM-1 levels.[64]

Markers of inflammation have also been shown to be elevated In GDM compared with that in women with a norm al pregnancy h1story.[10,30] C-reactive protem (CRP), [65-67] fibrinogen,[66] and plasminogen activator inhibitor-1[65] were observed to be elevated or specifically associated with GDM populations. Additionally, a prospective study of women from the second trimester until after delivery revealed an elevated CRP association with increased risk for developing GDM, even after adjusting for maternal prepregnancy BM1,[67] contrary to a prior report.[68]

## Autonomic Dysfunction

Gasic et al[69] studied cardiac autonomic dysfunction as revealed through alterations in heart rate variability. He performed 24-hour Holter monitoring on 48 healthy women with a history of GDM and assessed heart rate variability in both low-frequency as well as high-frequency domains. The investigators observed that 52% of women with a history ofGDM in the prior 1.0 ± 0.3 years were found to have sympathetic and parasympathetic autonomic neuropathy reflected in reductions of lowand high-frequency power spectral densities, respectively. An earlier study of autonomic dysfunction in women with an 8-year history ofGDM also revealed both parasympathetic and sympathetic autonomic neuropathy, but this population included women who had diabetes or glucose intolerance at the time of study?[70]

## CARDIOVASCULAR DISEASE .MANIFESTATIONS

### Coronary Artery Disease and Cardiovascular Events

Given this significant impact of T2DM on the risk for developing CVD, Carr et al[32] examined a population of women from the Genetics of Non-Insulin Dependent Diabetes Study[71] who had a first-degree relative with T2DM. The women were divided into two groups: those who had a history of GDM ($n$ = 332) and those who did not ($n$ = 662). The women were all similarly obese, but the women with GDM were younger and more often premenopausal than the controls. Nonetheless, the OR of self-reported CVD, defined as coronary artery disease (CAD) and/or stroke, was greater among the GDM women than among the controls, even after adjusting for age and menopausal status (OR, 1.85; 95% Cl [1.21 to 2.82]). Moreover, the similarly adjusted OR of CAD was higher among women with a GDM history (OR, 1.58; 95% Cl [1.00 to 2.49]) and was diagnosed at an earlier age than CAD among the women with no GDM history (45.5 ±2.2 years vs. 52.5 ± 1.9 years; $p$=0.02).

Additionally, the increased OR for CVD remained even after adjusting for metabolic syndrome (OR, 1.74; 95% Cl [1.10 to 2.76]) orT2DM (OR, 1.56; 95% Cl [1.00 to 2.43]). Although this study is limited by the self-reporting of GDM and CVD history, it does provide intriguing evidence that GDM may confer additional CVD risk above and beyond the CVD risk associated with obesity, the metabolic syndrome, and T2DM.

Another investigation ofCVD events after GDM was performed by Shah et al,[72] who conducted a retrospective matched-cohort study of an administrative database of a Canadian population including 8191 women with a history of GDM and 81,262 controls followed for a median of 11.5 years, and the authors observed a hazard ratio of 1.71 (95% Cl [1.08 to 2.9]) for CVD including CAD events that decreased to 1.13 (95% Cl [0.67 to 1.89]) after adjusting for the development of T2DM. Although CVD risk was more attributable to T2DM in this cohort, the hazard ratio is in the range reported by Carr et al?[32]

### Cardiac Dysfunction

Cardiac dysfunction resulting from GDM has been examined in the setting of diastolic dysfunction in a study of 13 women with GDM and 13 normoglycemic women studied during the third trimester and again 2 months after delivery.[73] The women with GDM were noted to have significantly decreased rapid filling to late filling time ratios both during and after pregnancy. In addition, tissue Doppler parameters revealed a lower lateral mitral annulus early diastolic velocity (Em), lower Em/lateral mitral annulus early diastolic velocity (Am), and higher Am that remained postpartum. These data suggest that these women with GDM, whose mean age was only 30.2 ± 5.9 years, manifested evidence of diastolic dysfunction not observed among the control women. However, this study was not designed to determine if these tissue Doppler abnormalities were associated with overt CVD.

Oren et al[27] also performed two-dimensional M-mode echocardiography on women in the third trimester of pregnancy who were normotensive, hypertensive, or had GDM. The echocardiograms revealed the GDM women had a significantly greater left ventricular mass

compared with that of the hypertensive and the normotensive women, primarily due to left ventricular dilatation rather than septal or posterior wall thickness. The GDM and hypertensive women also had impaired left ventricular relaxation but maintained normal ejection fraction and cardiac output.

## CONCLUSIONS

GDM represents a significant risk factor for the development of CVD in women; both patients and physicians need to be aware of not only intrapartum but also postpartum and lifetime risks. An initial focus of CVD risk management for this population of women should be on reducing the risk of progression to T2DM postpartum, as well as efforts to minimize modifiable CVD risk factors, including blood pressure, abdominal adiposity, and dyslipidemia. Ideally, these efforts will incorporate both prenatal and postpartum education about risk awareness, healthy lifestyle behaviors, breast-feeding, and potential pharmacotherapy options.[74] Future investigations may address how best to use information regarding biochemical and subclinical CVD evidenced in clinical investigations in primary prevention endeavors.

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## Table 1

Parameters Examined in GDM

- **Cardiovascular Disease Risk Factors**
  - Type 2 diabetes mellitus
  - Blood pressure
  - Lipid profile
  - Metabolic syndrome
- **Cardiovascular Disease Surrogate Measures**
  - **Endothelial Dysfunction**
    - Brachial artery flow-mediated vasodilation
    - Carotid artery intimal-medial thickness
  - **Biochemical Markers**
    - E-selectin
    - Vascular adhesion molecule-1
    - Intercellular adhesion molecule-1
  - **Inflammatory Markers**
    - C-reactive protein
    - Fibrinogen
    - Plasminogen activator inhibitor-1
  - **Autonomic Dysfunction**
    - Heart rate variability
- **Cardiovascular Disease Manifestations**
  - **Coronary Artery Disease and Cardiovascular Events**
  - **Cardiac Dysfunction**
    - Tissue Doppler parameters
      - Diastolic velocity
    - Two-dimensional M-mode echocardiography
      - Left ventricular mass