

Gestational Diabetes and the Risk of Cardiovascular Disease: A Systematic Review

Short title: Gestational Diabetes and Cardiovascular Disease

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ABSTRACT

Background: Gestational diabetes mellitus (GDM) is associated with an increased risk of incident type 2 diabetes and has deleterious effects on other cardiovascular risk factors. However, the effect of GDM on the risk of cardiovascular disease (CVD) remains unclear. We therefore conducted a systematic review of observational studies examining the association between GDM and CVD.

Methods: We systematically searched Embase and Medline for observational studies examining the association between GDM and CVD. We restricted our search to studies of humans and those published in English or French. Outcomes of interest included angina, arrhythmia, coronary artery disease, heart failure, myocardial infarction, stroke, and composite endpoints with these outcomes. We assessed the quality of included studies using the Newcastle-Ottawa scale for observational studies.

Results: A total of 4 studies (2 cross-sectional and 2 cohort studies) met our inclusion criteria. The two cohort studies were conducted in overlapping study populations. After adjusting for potential confounders, the relative risk for incident CVD ranged from 1.66 (95% confidence interval [CI] = 1.30, 2.13) to 1.85 (95% CI = 1.21, 2.82). Further adjustment for subsequent type 2 diabetes mellitus attenuated the effects but with wide 95% CIs that included unity (range: 1.13 [95% CI = 0.67, 1.89] to 1.56 [95% CI = 1.00, 2.43]).

Conclusion: Available data suggest that GDM is associated with an increased risk of CVD. However, available data are limited, and evidence regarding this association independent of the increased risk due to subsequent type 2 diabetes remains inconclusive.

Keywords: Gestational Diabetes, Pregnancy, Heart Diseases, Systematic Review, Observational Studies.

INTRODUCTION

Gestational diabetes mellitus (GDM) occurs in approximately 7% of all pregnancies in North America¹. The majority of women who develop GDM return to pre-pregnancy glycemic levels during the postpartum period, but studies have established a strong association between GDM and an increased risk of developing type 2 diabetes mellitus later in life^{2,3}. In addition, women with GDM are more likely to later develop obesity, dyslipidemia, and hypertension than women without GDM^{4,5}. However, the effect of GDM on the risk of cardiovascular disease (CVD) remains unclear. It is also uncertain if any association between GDM and CVD is independent of the increased risk of type 2 diabetes mellitus. We therefore conducted a systematic review to examine the association between GDM and CVD and the role of type 2 diabetes mellitus in any observed association.

METHODS

Data Sources

We systematically searched Embase and Medline from inception to June 5th, 2012 for observational studies examining the association between GDM and adverse cardiovascular outcomes. Medical Subject Heading (MeSH) terms and key words for GDM (gestational diabetes, pregnancy-induced diabetes) were combined with those for CVD (acute coronary syndrome, cardiovascular disease, cardiovascular pregnancy complications, coronary artery disease, heart attack, myocardial infarction, pregnancy complications, stroke, and unstable angina); our search strategy is reported in detail in Appendices 1 and 2. We also restricted our search to studies conducted in humans and to those published in English or French. Using Health Information Research Unit (HIRU) etiology search filters (hedges)⁶, we further restricted

our search to observational studies using the filter that achieves the best balance of specificity and sensitivity. Finally, we hand-searched the references of relevant reviews to identify additional studies not identified in our electronic search.

Our systematic review was conducted following a pre-specified protocol and the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement⁷.

Study Selection

We included studies if: 1) the study population was pregnant women stratified by the presence or absence of self-reported or clinically-diagnosed GDM; 2) the study reported CVD as an outcome (e.g., acute coronary syndrome, arrhythmia, coronary artery disease, heart failure, myocardial infarction, stroke, unstable angina, or a composite of these endpoints) by GDM status; 3) the study was conducted in humans; 4) the study was published in English or French; and 5) the study design was observational, including cohort, case-control, cross-sectional, or hybrid designs.

We excluded animal studies and those conducted in women with a known history of cardiovascular disease. Conference abstracts were excluded as these publications do not undergo rigorous peer-review and their results are often preliminary in nature. Finally, we excluded all reviews, commentaries, editorials, letters to the editor, and poster summaries.

Data Extraction

Data extraction was conducted independently by 2 reviewers, with disagreements resolved by consensus or, when necessary, by a third reviewer. For each study, reviewers extracted information regarding study design and period, the country where the study was conducted, demographic and clinical characteristics of the study population, the prevalence of

GDM, and CVD events. Our primary outcome of interest was CVD, and we extracted the definition used in each study. Additional events of interest included angina, arrhythmia, coronary artery disease, heart failure, myocardial infarction, and stroke. Outcomes were extracted as count data and crude effect measures (i.e., odds ratios [OR], hazard ratios [HR]) with corresponding 95% confidence intervals (CIs). Crude effect measures and 95% CIs were calculated from reported count data when necessary. In addition, we extracted the results of multivariable analyses that adjusted for potential confounders as well as those that adjusted for subsequent type 2 diabetes mellitus. When necessary, we contacted the authors of included studies to resolve ambiguities and obtain additional information.

Quality Assessment

The quality of each included study was assessed independently by two reviewers using the Newcastle-Ottawa Scale (NOS) for nonrandomised studies⁸, with disagreements resolved by consensus or by a third reviewer. The NOS was developed to evaluate case-control and cohort studies based on three broad perspectives: the selection of the study group, the comparability of the groups, and the ascertainment of outcome/exposure. For cross-sectional studies, we applied the NOS version (i.e., case-control vs cohort) that was most consistent with how the data were reported in the original manuscript.

RESULTS

Search Results

Our initial search of Embase and Medline identified 7,442 potentially relevant publications (Figure 1). Following the removal of 2,426 duplicates, we excluded 4,920 publications during title/abstract screening and examined the full texts of the remaining 97

articles. A total of four studies met our inclusion criteria and were included in our systematic review.

Cross-Sectional Studies

A total of four studies met our inclusion criteria, including two cross-sectional studies^{9;10} and two cohort studies^{11;12} (Table 1). In the two cross-sectional studies, Carr et al.¹⁰ and Freibert et al.⁹ examined the association between a self-reported history of GDM and CVD endpoints through self-administered questionnaires. The study by Carr et al. was conducted in women with a family history of type 2 diabetes (n=994)¹⁰, and the study by Freibert et al. was conducted in women participating in the Kentucky Women's Health Registry (n=3,909)⁹. Both studies included American women of approximately 50 years of age^{9;10} and examined composite CVD endpoints, the components of which are listed in Table 2.

Study quality was comparable in both cross-sectional studies, with both studies receiving Newcastle-Ottawa scores of 4 (Appendices 3 and 4). Due to their cross-sectional designs, neither study received stars for adequacy of follow-up or for ensuring that the outcome was not present prior to exposure assessment. Furthermore, in both studies, the presence of GDM and CVD was only assessed via self-administered questionnaire and due to the study design, it was not possible to ascertain the temporality of the GDM and CVD.

In the study by Freibert et al.⁹, women with a history of GDM had a substantially greater prevalence of CVD than those with no history of GDM or other self-reported pregnancy complications, including preterm labor, pre-eclampsia, or third trimester bleeding (43.8% vs 22.4%, difference = 21.4%, 95% CI = 13.2, 29.6)(Table 2). In the study by Carr et al.¹⁰, there was no difference in the crude prevalence of CVD by GDM status (15.5% vs 12.5%, difference = 3.0%; 95% CI = -1.6, 7.8). However, GDM was associated with an increased prevalence of

CVD after adjusting for potential confounders, including age, menopausal status, and clustering on the proband (OR = 1.85, 95% CI = 1.21, 2.82). Further adjustment for type 2 diabetes attenuated the association (OR = 1.56, 95% CI = 1.00, 2.43).

In secondary analyses, Carr et al. stratified their results by race¹⁰. Although there was some variability in the point estimate of the association between GDM and the prevalence of CVD, all 95% CIs were wide and overlapping (Caucasians: OR = 1.62, 95% CI = 0.84, 3.12; African American: OR = 1.27, 95% CI = 0.62, 2.61; Latina: OR = 2.91, 95% CI = 1.06, 8.02).

The components of the CVD composite endpoints were examined individually in the two cross-sectional studies^{9;10}(Table 3). After adjusting for potential confounders, GDM was associated with increased odds of angina, arrhythmia, CAD, and myocardial infarction. The examination of the associations with heart failure and stroke were inconclusive due to wide 95% CIs.

Cohort Studies

The two cohort studies were conducted using administrative data from the Canadian province of Ontario during overlapping study periods^{11;12} (Table 1). Shah et al. examined the effect of GDM on the risk of incident CVD between April 1994 and March 1997¹² while Retnakaran et al. examined women with GDM between April 1994 and March 1998¹¹. In the former, the primary exposure was GDM whereas, in the latter, mild glucose intolerance was the primary exposure and GDM was a secondary exposure category. In both studies, patients with a previous diagnosis of non-gestational diabetes (i.e., type 1 or type 2 diabetes) were excluded. Both studies also restricted inclusion to pregnancies that resulted in a live birth, and randomly selected one pregnancy per woman. The median follow-up in both cohort studies was greater than 10 years, and the sample sizes were 89,262 and 363,865 women, respectively. The two

cohort studies involved women of approximately 30 years of age^{11,12}. In the study by Shah et al.¹², women with a history of CVD were excluded. Although this was not an exclusion criteria in the study by Retnakaran et al.¹¹, the proportion of women with a history of CVD that were included in the study was exceedingly small (B. Shah, personal communication, July 24, 2012).

Not surprisingly, the cohort studies were of higher quality than the cross-sectional studies (Appendix 3), with both Retnakaran et al.¹¹ and Shah et al.¹² receiving 8 out of 9 possible stars. Retnakaran et al.¹¹ did not exclude women with a previous history of CVD and thus received only 3 of 4 stars for patient selection. In addition, Shah et al. did not adjust for potential confounders other than subsequent diabetes and thus received a score of 1 out of 2 stars for comparability. Although neither cohort study reported the completeness of follow-up, both received a star for this criterion as the authors used population-based administrative data, and it is unlikely that bias occurred due to patients leaving the province differentially.

As with the cross-sectional studies, composite endpoints were used (Table 2). In the cohort studies, the composite endpoint components included admission to hospital for myocardial infarction, coronary artery bypass, coronary angioplasty, stroke, or carotid endarterectomy. In the study by Retnakaran et al., women with GDM had a higher crude CVD rate than women without GDM (4.2 vs 1.9 per 10,000 person-years, respectively)¹¹. After adjustment for potential confounders, GDM remained associated with a higher rate of incident CVD (HR = 1.66, 95% CI = 1.20, 2.13). However, further adjustment for subsequent type 2 diabetes attenuated this association and produced estimates that included both null and clinically important effects (HR = 1.25, 95% CI = 0.96, 1.62). Similar results were obtained in the cohort study by Shah et al.¹²

DISCUSSION

Our study was designed to systematically review all observational studies examining the association between GDM and CVD and examine the role of subsequent type 2 diabetes in this relationship. We identified four studies examining this association, and their data suggest that GDM is independently associated with a substantial increase in the risk of CVD. Further adjustment for subsequent diabetes attenuated the association and resulted in point estimates that were accompanied by imprecise 95% CIs that included both unity and clinically important increased risks in both cohort studies^{11;12}. Thus, evidence regarding a potential increased risk of incident CVD independent of the increased risk of subsequent type 2 diabetes remains inconclusive.

One of the key findings of this systematic review is that high quality evidence regarding the effect of GDM on the risk of CVD is limited. Only four studies have examined this association to date, and these four include two cross-sectional studies that relied on self-reported exposure and outcome assessment^{9;10} and two underpowered cohort studies with overlapping study populations^{11;12}. Furthermore, all included studies were likely affected by residual confounding. For example, there was no adjustment for obesity, an important risk factor for both GDM⁴ and CVD¹³. Given the limitations of cross-sectional studies (e.g., temporal ambiguity, prevalent cases), there also remains a need to examine the effect of GDM on the incidence of individual CVD endpoints using longitudinal data. Finally, the effect of GDM on the risk of incident CVD independent of traditional CVD risk factors (including type 2 diabetes) warrants further investigation, as does the role of GDM in the risk stratification of women for CVD. Both cohort studies assessed the mediating effects of type 2 diabetes by including it as a covariate in their regression analyses, which can result in biased estimates^{14;15}. The use of causal inference techniques such as marginal structural models¹⁶ is needed to address this potential mediation.

To our knowledge, this is the first systematic review examining the association between GDM and CVD events. Previous reviews have addressed the association between GDM and CVD risk factors, such as hypertension, dyslipidemia, obesity, and blood pressure¹⁷⁻²⁰. These reviews found that GDM had harmful effects on these CVD risk factors. For example, Bentley-Lewis et al. found that women with GDM had a higher risk of gestational hypertension than women without GDM (OR = 1.34; 95% CI = 0.49, 3.71)²¹. In addition, Fraser et al. found that women with GDM had higher body mass index (5.25 kg/m²), waist circumference (13.18 cm), systolic blood pressure (5.12 mm Hg), and fasting glucose (2.58 mmol/L) than women without GDM⁴. While these previous reviews did not address the effect of GDM on hard CVD endpoints, their results are consistent with those of the present review.

Our study has a number of strengths. First, our systematic review followed a pre-specified protocol. Second, we contacted the authors of included studies to obtain additional information and resolve important ambiguities regarding included studies. Third, our systematic review was conducted and reported following the guidelines set forth in PRISMA⁷.

Our systematic review also has some potential limitations. First, due to important heterogeneity in study design, overlapping study populations, and limited available data, we were unable to meta-analyze data across studies. Second, our search was restricted to studies published in English or French. This decision was made for practical reasons. Furthermore, we elected to exclude abstracts and conference proceedings as such publications do not undergo the same rigorous peer-review as full-length articles. This restriction to studies published in English or French may have resulted in language and/or publication bias. Finally, the study question is an etiologic one, and we were thus limited to the use of observational data. The possible effects of residual confounding must therefore be considered when interpreting these data.

CONCLUSION

Our systematic review of the available literature suggests that GDM is associated with an increased risk of CVD. However, available data are limited. Our examination of the role of subsequent diabetes in influencing this association indicates that the increased CVD risk is likely partly mediated by an increased risk in subsequent diabetes, but this evidence remains inconclusive due to sparse data.

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DISCLOSURES

The authors have no relationships to disclose.

CONTRIBUTION OF AUTHORS

Mr. Archambault conducted the literature search and data extraction, interpreted data, and is the principal author of the manuscript. Dr. Filion contributed to the study conception and design, interpretation of data, and writing of the manuscript. Dr. Filion also supervised the conduct of the study. Dr. Arel contributed to the interpretation of data and critically reviewed the manuscript for important intellectual content. All of the authors approved the final version of the manuscript. Dr. Filion is the guarantor.

Table 1. Study and baseline patient characteristics of studies examining the association between gestational diabetes mellitus and the risk of cardiovascular disease.

Study	Year of Publication	Country	Data Source	Study Period	Sample Size (%)		Age (years)*		Median Follow-up (years)
					GDM	no GDM	GDM	no GDM	
<u>Cross-sectional studies:</u>									
Carr et al.	2006	USA	GENNID Study	1993-2001	332 (33.4)	662 (66.6)	48.6 ± 0.7	52.4 ± 0.6	-
Freibert et al.	2011	USA	Kentucky Women's Health Registry	2006-2008	146 (4.4)	2,558 (77.4) [†]	57.1 ± 5.5	60.3 ± 7.5	-
<u>Cohort studies:</u>									
Retnakaran et al.	2009	Canada	Ontario Administrative Claims Database [‡]	April 1994-March 1998	13,888 (3.2)	349,977 (80.3) [§]	31.1	29.2	12.5
Shah et al.	2008	Canada	Ontario Administrative Claims Database [‡]	April 1994-March 1997	8,191 (9.2)	81,262 (90.8)	-	-	11.3

Abbreviations: GDM: Gestational Diabetes Mellitus; GENNID: Genetics of Non-Insulin dependent Diabetes. *Age presented as mean ± standard deviation. [†]The non-gestational diabetes group was defined as patients with no history of preterm labor, pre-eclampsia, gestational diabetes, or third trimester bleeding. A total of 598 women (18.1%) reported having a history of these other pregnancy complications with no history of gestational diabetes. [‡]Administrative claims databases included population-based discharge abstract data, physician service claims, and demographic data. These data were linked to the Ontario Diabetes Database to exclude those with a pre-gestational history of diabetes. [§]The non-gestational diabetes group was defined as patients who did not receive an antepartum glucose tolerance test. A total of 71,831 women (16.5%) received an antepartum glucose tolerance test, suggesting the presence of an abnormal glucose challenge test result, but did not have gestational diabetes. ^{||}Mean age for all participants was 31 years old.

Table 2. Effect of gestational diabetes mellitus on the risk of cardiovascular disease.

Cardiovascular Disease (CVD)						
Study	CVD Definition	n (%) - GDM	n (%) - no GDM	Effect Measure*		
				Crude (95% CI)	Adjusted (95% CI)	Adjusted for Subsequent Diabetes (95% CI)
<u>Cross-sectional studies:</u>						
Carr et al.	Self-reported history of coronary artery disease, or stroke	51/329 (15.5)	81/653 (12.5)	1.30 (0.89, 1.89)	1.85 (1.21, 2.82) [‡]	1.56 (1.00, 2.43) [§]
Freibert et al.	Self-reported history of angina, heart attack, heart failure, or arrhythmia	64/146 (43.8)	573/2558 (22.4) [†]	2.70 (1.93, 3.80)	-	-
<u>Cohort studies:</u>						
Retnakaran et al.	Admission to hospital for acute myocardial infarction, coronary artery bypass, coronary angioplasty, stroke, or carotid endarterectomy	-	-	-	1.66 (1.30, 2.13) [‡]	1.25 (0.96, 1.62)
Shah et al.	Admission to hospital for acute myocardial infarction, coronary artery bypass, coronary angioplasty, stroke, or carotid endarterectomy	-	-	1.71 (1.08, 2.69)	-	1.13 (0.67, 1.89) [¶]

Abbreviations: GDM: Gestational Diabetes Mellitus; CI: Confidence Interval; CVD: Cardiovascular Disease. *Odds ratios are reported for cross-sectional studies, and hazards ratios are reported for cohort studies. [†]The non-gestational diabetes group was defined as patients with no history of preterm labor, pre-eclampsia, gestational diabetes, or third trimester bleeding. [‡] Odds ratio adjusted for age and menopausal status and clustering on the proband. Subsequent analyses adjusted for age, menopausal status, and race/ethnicity (OR = 1.66; 95% CI = 1.07, 2.57). [§]Odds ratio adjusted for type 2 diabetes and proband status. [‡]Hazard ratio adjusted for age, year of delivery, rural residence, income, comorbidity, pre-existing hypertension, and gestational hypertension. [¶]Shah et al. did not adjust for potential confounders other than subsequent diabetes.

Table 3. Association between gestational diabetes and individual cardiovascular endpoints.

Event	Study	n (%) - GDM	n (%) - no GDM	Crude OR (95% CI)	Adjusted OR (95% CI)*
Angina	Freibert et al.	17 (11.6)	113 (4.4)	2.85 (1.66, 4.89)	2.90 (1.50, 5.60) [†]
Arrhythmia	Freibert et al.	41 (28.1)	386 (15.1)	2.20 (1.51, 3.20)	2.40 (1.50, 3.70) [†]
Coronary Artery Disease	Carr et al.	40 (12.2)	70 (10.7)	1.29 (0.71, 2.32)	1.58 (1.00, 2.49) [‡]
Heart Failure	Freibert et al.	1 (0.7)	28 (1.1)	0.62 (0.08, 4.61)	0.70 (0.10, 5.60) [†]
Myocardial Infarction	Freibert et al.	5 (3.4)	46 (1.8)	1.94 (0.76, 4.94)	3.40 (1.10, 11.30) [†]
Stroke	Carr et al.	19 (6.2)	31 (4.9)	1.15 (0.76, 1.74)	1.67 (0.87, 3.22) [‡]

Abbreviations: GDM: Gestational Diabetes Mellitus; OR: Odds Ratio; CI: Confidence Interval. *Both studies examining individual endpoints were cross-sectional. [†]Odds ratios were adjusted for age, education, and smoking status. The reference group in the study by Freibert et al. was never-pregnant women. Compared with never-pregnant women, women with a history of pregnancy but no history of GDM had adjusted odds ratios of 1.10 (95% CI = 0.70, 1.8) for angina, 1.10 (95% CI = 0.90, 1.50) for arrhythmia, 0.80 (95% CI = 0.30, 1.90) for heart failure, and 1.50 (95% CI = 0.70, 3.20). [‡]Odds ratios adjusted for age, menopausal status, and clustering on the proband.

FIGURE LEGEND

Figure 1. PRISMA flow diagram describing the systematic literature search for studies examining the association between gestational diabetes mellitus and incident cardiovascular disease.