Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 6 Issue 7 July 2022

Research Article

Risk of Developing CVD in Women with a History of Gestational Diabetes

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DOI: 10.31080/ASMS.2022.06.1315

Received: February 21, 2022

Published: June 10, 2022

Abstract

Aims: Despite significant improvements in cardiovascular care over the past decades, cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in men and women globally. Apart from traditional CVD risk factors, some gender-specific conditions contribute to the risk of CVD in women. This review investigates the relationship between gestational diabetes mellitus and CVD risk in women.

Methods: The search for the literature was conducted in MEDLINE, CINAHL, and Cochrane library, and was limited to articles published in English between January 2015 and 2020. Following the application of the study inclusion and exclusion criteria, eight studies were included in the review.

Results: The findings of this review suggest that the risk of future CVD events is higher in women with a history of gestational diabetes. The findings support the need for early cardiovascular assessment and risk factor management after the postpartum period among women with gestational diabetes.

Conclusions: Health care providers should be aware of the association between gestational diabetes and CVD risk and develop health promotion strategies to reduce the risk among this high-risk women group.

Keywords: Cardiovascular Disease; Coronary Artery Disease; Gestational Diabetes Mellitus

Introduction

Cardiovascular disease (CVD) is the primary cause of death globally, and more people die from different types of CVD than any other group of diseases every year. In 2016, almost 17.9 million people died from CVD, representing 31% of all deaths worldwide, and 85% of those deaths were due to myocardial infarction (MI) and stroke [1]. In the United States (US), CVD remained the leading cause of death, responsible for over 800,000 deaths in 2016 [2]. In line with international trends, CVD was the main cause of death, accounting for 26% of all deaths in 2018 in Australia [3]. Of these, 42% were due to coronary artery disease, 20% stroke, and 10% heart failure and cardiomyopathy [3]. The prevalence of CVD among Australians was about one in twenty (4.8%) in 2017-2018 [4]. In developing countries, the burden of the CVD is even higher and rising, accounting for more than 75% of all deaths [1].

A variety of modifiable and non-modifiable risk factors are responsible for developing CVD in both men and women [5]. Non-modifiable risk factors include gender, age, family history, ethnic background, previous myocardial infarction, and known modifiable risk factors are: hypertension, hypercholesterolemia, diabetes, obesity, and dyslipidemia, smoking, and physical inactivity [5]. While most CVD risk factors are shared between men and women,

some risk factors risk factors affect women strongly or are solely. For example, diabetes is known to be a stronger risk factor for developing CVD in women than men [6] and having a history of pregnancy loss or hypertensive disorders in pregnancy is exclusive to women [7,8].

This article aims to review the risk of CVD in women with a history of gestational diabetes mellitus (GDM). GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy [9]. Management of GDM depends on the severity of the condition and includes diet and lifestyle modifications with or without medication therapy (American Diabetes Association, 2004). Worldwide, the prevalence of GDM varies between 1% - 28%, with trends indicating growth during the last decades [10]. Variances in screening and diagnostic criteria account for the wide prevalence rates across studies [10]. International Diabetes Federation (2020) reported that one in six pregnancies was affected by GDM in 2019 [11].

GDM is associated with increased risk of developing type two diabetes in women in the future, which is a strong risk factor for CVD [12]. The risk of CVD is more than double in individuals with diabetes compared to those without diabetes [12]. Evidence also suggests that the impact of diabetes on CVD risk is greater in women than men [6]. Women with a history of diabetes show a 40% increased risk of CHD and 25% increased risk of stroke [6].

Subjects, Materials and Methods

Search strategy

The literature on the associations between GDM and CVD risk was accessed through a systematic search of MEDLINE, CINAHL, and Cochrane library using predefined search terms. The search was limited to the English language and to publication years January 2015 to March 2020. The search terms for exposure included: gestational diabetes mellitus, gestational diabetes, GDM, and outcome terms were: cardiovascular disease, heart disease, coronary heart disease, coronary artery disease, myocardial infarction, acute coronary syndrome, ischaemic heart disease, and ischemic heart disease. All primary studies that examined association between GDM and the risk of developing CVD in later life were included. Review articles and conference papers were excluded.

Study selection

The process of study selection is presented in figure 1. A total of 92 articles were retrieved from the initial search. After limiting to the English language and the defined years of publication, the search yielded 61 citations. Review articles, conference papers, and duplications were removed, leaving 40 articles. Initial screening of the title of the articles and their abstracts resulted in the exclusion of 24 articles, leaving 16 papers for further assessment. The full texts of the studies were reviewed for relevancy, resulting in the exclusion of further eight articles. The remaining eight articles were included in this study (Figure 1).

Figure 1: PRISMA flow diagram of the literature search.

Results

Of the eight included articles, six studies were large population-based cohort studies (n = 4,685,808), one study was a cross-sectional study, and one a case-control study (n = 6880). Three studies were conducted in Canada, two in the US, and one each in the United Kingdom (UK), France, and Israel (Table 1).

A retrospective population based cohort study in the UK (Daly., *et al*. 2018) identified 9,118 women diagnosed with GDM

First author	Sample size	Study design	Follow up period	Risk of CVD and T2D after previous GDM
Daly., et al. (2018) The UK	n = 46,399 (exposed group n = 9,118, control group = 37,281)	Retrospective cohort	26.3 years	Higher risk IHD (IRR 2.78;95% CI 1.37-5.66) T2DM (IRR 21.96;95% CI 18.31-26.34)
McKenzie-Sampson., et al. (2018) Canada	n = 1,070,667 (exposed group n = 67,356, control group n = 1,003,311	Retrospective cohort	25.2 years	Higher risk IHD (HR 1.23;95% CI 1.12-1.36) MI (HR 2.14;95% CI 1.15-2.47)
Retnakaran and Shah (2017) Canada	n = 1,515,079	Population- based cohort(longitudinal)	10.0 years	Higher risk CVD (HR 2.82;95% CI 2.41-3.30;P Value <0.0001) MI (HR 3.54;95% CI 2.96-4.23;P Value <0.0001)
Tobias., et al. (2017) The US	n = 89,479	Prospective cohort (longitudinal)	25.7 years	Higher risk CVD (HR 1.43;95% CI 1.12-1.81 MI (HR 1.59;95% CI 1.16-2.17) T2D (HR 4.02;95% CI 1.94-8.31)
Shostrom., et al. (2017) The US	n = 8217	Population-based cross-sectional survey	7 years	Higher risk CVD (OR 1.63;95% CI 1.02-2.62;P Value 0.04)
Goueslard., et al. (2016) France	n = 1,518,990	population-based retrospective (longitudinal)	7 years	Higher risk CVD (aOR 1.25;95% CI 1.09-1.43) MI (aOR 1.92;95% CI 1.36-2.71)
Charach., et al. (2016) Israel	n = 6880 (exposed group = 815, control group = 6065)	Retrospective case-control	6.2 years	Higher risk Atherosclerotic (HR 1.29;95% CI 1.1-1.5;P Value <0.003)
Kaul., et al. (2015) Canada	n = 474,348	Retrospective cohort	5.3 years	Higher risk CVD (aHR1.4 ;95% CI 1.0-1.9) DM (aHR 20.3; 95% CI 18.1-22.6)

Table 1: Summary of the reviewed studies.

IRR, Incident Rate Ratio; HR, CI, Confidence Interval; OR, Odds Ratio; aOR, Adjusted Odds Ratio; CVD Hazard Ratio; aHR, Adjusted Hazard Ratio; IHD, Ischemic Heart Disease; MI, Myocardial Infarction; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; T2DM, Type II Diabetes;

between 1 February 1990 and 15 May 2016, using a large primary care dataset. The researchers matched these women with four pregnant women groups without GDM (n = 37,281) by age and timing of pregnancy. Women younger than 50 years old and all pregnancies were included. The findings of this research revealed that compared with women without GDM, the risk of developing IHD was 2.5 times higher in those with GDM (relative risk = 2.78; 95% confidence interval (CI)1.37-5.66; p-value = 0.005) [13]. Similarly, in a retrospective cohort study conducted in Quebec, Canada, McKenzie-Sampson., *et al.* (2018) enrolled 1,070,667 women who had live births in hospitals within 1989 to 2013. They identified 67,356 women with GDM and 1,003,311 without this history and followed them up for a maximum of 25.2 years after index pregnancy to compare CVD events in those groups [14]. The study established a positive relationship between GDM and risk of future CVD, including IHD (hazard ratio 1.23; 95% CI 1.12-1.36), MI (hazard ratio 2.14; 95% CI 1.15-2.47), and coronary angioplasty (hazard ratio 2.23; 95% CI 1.87-2.65) [14].

In a large population-based cohort study in Ontario, Canada, Retnakaran., *et al*. (2017) recruited 1,515,079 women, 15-54 years old, who delivered between April 1994 and March 2014, using the health care administrative database. Among these women 56,884 women were diganoised with GDM. After a median follow up of 10 years, the risk of CVD was found to be higher among women with a history of GDM, irrespective of developing type two diabetes mellitus (T2DM) after index pregnancy. The hazard ratios of CVD in women with and without T2DM were 2.82 (CI 2.41-3.30; p value <0.0001), and 1.30 (CI 1.07-1.59; p-value = 0.008), respectively, compared to women without a history of GDM. The risk of CHD was also higher in both groups (hazard ratio 3.54; CI 2.96-4.23; p-value <0.0001; and hazard ratio 1.41; CI 1.11-1.80; p value = 0.005, respectively) [15]. Likewise, Tobias., *et al*. (2017) in the US investigated long-term CVD events in women with a history of GDM using data from the Nurses' Health Study II. This longitudinal prospective cohort study was conducted between 1989 and 2015, and included 116,430 nurses aged between 24 and 44. Data were collected via questionnaire at baseline and subsequently every two years. In total, 89,479 nurses with self-reported GDM in at least one pregnancy, who did not have CVD and cancer at baseline were eligible for inclusion in the analysis [16]. The study found that GDM was positively associated with CVD development later in life. Compared with parous women without GDM, those with GDM experienced a 60% greater CVD events during the follow-up period (hazard ratio 1.60; 95% CI 1.26-2.04; p-value <0.001). However, adjustment for potential confounding factors reduced the association in this study (hazard ratio 1.29; 95% CI: 1.01-1.65; p value = 0.04). Analysing the data for MI and stroke separately, GDM was positively correlated with the development of MI in the fully adjusted model (hazard ratio 1.45;95% CI, 1.05-1.99; p value = 0.02), but there was found no correlation with stroke [16].

Using the National Health and Nutrition Examination Survey data in the US, Shostrom., *et al*. (2017) examined the association of the previous GDM with the risk of CVD in 8,127 parous women, 20 years of age and older, from 2007 to 2014 [17]. They found an increased risk for developing CVD in women with a history of GDM compared with those without GDM. The study showed that a history of GDM was associated with 63% higher odds of CVD events (odds ratio 1.63; 95% CI 1.02-2.62; p value = 0.04) after adjusting for demographic, socioeconomic, and lifestyle factors. Further adjustment for body mass index (BMI) moderately reduced this association (odds ratio 1.52; 95% CI 0.95- 2.44; p value = 0.08) [17].

In a nationwide population-based retrospective study in France, Goueslard., *et al*. (2016) used the French medico-administrative database to recruit women who gave birth between 2007 and 2008 [18]. Among 1,518,990 deliveries recorded in that period, 62,958 women had developed GDM. After 7 years of follow up, the study found that GDM was significantly associated with a higher risk of CVD (adjusted odds ratio = 1.25; CI 1.9-2.20) and MI (adjusted odds ratio = 1.92; CI 1.36-2.71). In this study, the researchers adjusted for age, diabetes mellitus, body mass index (BMI), and history of hypertensive disorders in pregnancy [18].

Charach., *et al*. (2016) carried out a retrospective case-control study in Israel to examine the association between glucose level during pregnancy and later development of long term maternal atherosclerotic morbidity, including CVD [19]. The researchers identified all women who delivered between 2000 and 2012 and subsequently developed atherosclerotic morbidity (n = 815). The researchers matched these women randomly by age and year of delivery (n = 6065) with women who did not develop GDM. After 74 months follow up, the study found a statistically significant association between glucose level during pregnancy and long-term atherosclerotic hospitalization (p < 0.001). This association was dose-response, in that the incidence of severe atherosclerotic morbidity was higher among women who had glucose levels greater than 5.5 mmol/l (hazard ratio 1.29; 95% CI 1.1- 1.5; p value = 0.003). The study concluded that an elevated glucose level during pregnancy, even within the range of slight glucose intolerance, may serve as a marker for future maternal atherosclerotic morbidity [19]. Finally, in another retrospective cohort study in Canada, Kaul., *et al*. (2015) recruited 474,348 women with singleton deliveries between April 1999 and March 2010 and categorized them according to their pre-pregnancy weight and GDM status [20]. With a median follow-up of 5.3 years, the study found that CVD incidence in women with GDM was 1.9% compared with 1.0% in control group. The risk of developing CVD was particularly higher in women who had a history of GDM and were overweight or obese [20].

Discussion and Conclusion

This review study highlights the impact of one of the most frequent complications in pregnancy, GDM, on women's

cardiovascular health. The studies included in this review were large cohort studies, and findings across the studies were consistent in showing that the risk of developing CVD later in their life was higher in women with a history of GDM compared to those without such history. Of further concern is that the risk manifested itself within as earlier as a decade after an index pregnancy [18]. Hence, the diagnosis of GDM offers an exceptional opportunity to detect young women who are at higher risk of CVD and therefore intervene appropriately to reduce their risk [21].

The underlying mechanisms for developing of pregnancy complications, including GDM, are not fully understood [22], however, it is well known that physiological changes during pregnancy impose stress on the cardiovascular system [23], for example, 30-50% increase in plasma volume, increased lipid levels, and a shift in glucose metabolism [21]. These physiological changes, along with advanced maternal age in recent years, seem to increase the likelihood of pregnancy complications and the associated long term adverse health effects [23]. Ferranti., *et al*. (2016) suggest that pregnancy may unmask some underlying metabolic and vascular abnormalities in women [21]. Although the physiological and metabolic changes during pregnancy return to pre-pregnancy levels shortly after delivery [23], even a normal glucose tolerance test shortly after GDM was found to be associated with developing various metabolic abnormalities [10].

In addition, a history of GDM is linked with increased cardio metabolic risk. Women with a history of GDM are more likely to develop hypertension and dyslipidaemia and have lower high-density lipoprotein cholesterol. They are also more likely to have higher fasting glucose within the first ten years after complicated pregnancy [24,25] and are at increased risk of developing T2DM, which a strong CVD risk factor [10,24]. Di Cianni., *et al*. (2018) reported that 10%-31% of parous women with a history of GDM develop type T2DM later in their life [10]. About 30%-50% of these women develop diabetes within 3-5 years postpartum and 70% within the first 10 years [13]. Although this partially explains the increased risk of CVD associated with GDM, at least one study (Retnakaran and Shah, 2017) reported that the CVD risk in women with a history of GDM was independent from T2DM. Also, the association between GDM and CVD remained significant when the effects of other risk factors, such as obesity, hypertension, family history, and hypercholesterolemia were controlled [23].

In 2011, the American Heart Association (AHA) recognized women with a history of GDM and hypertension disorders in pregnancy as high-risk group for CVD and suggested that appropriate and timely interventions are developed and implemented to the minimize this risk [10,26]. Lifestyle modification and pharmacological interventions have shown beneficiary effects on reducing CVD risk in high-risk groups [6], whether such interventions are also capable of reducing CVD risk in women with a history of complicated pregnancy, including GDM, yet to be investigated. These findings also indicate the necessity of adherence to diabetes prevention programs to prevent the risk of developing GDM and subsequent T2DM [27].

The results of this review highlight the importance of consideration of obstetric history in assessing CVD risk in women. Pregnancy provides a window of opportunity to undertake a glucose screen test to detect GDM, with positive results indicating an increased risk for developing T2DM and CVD in the future [28]. Women of reproductive age are relatively young women who may benefit from early interventions through regular monitoring, lifestyle modifications, and treatment to reduce CVD related morbidity and mortality in their later life [10,21]. Awareness of the link between GDM and CVD risk should be raised among women and health care providers through appropriate educational programs. Pregnancy provides a unique opportunity for healthcare professionals to play a vital role in assessing CVD risk in women and promoting a healthy lifestyle, as suggested by the American College of Obstetricians and Gynaecologists, to improve postpartum care [28]. Targeted interventions and long-term follow-up programs need to be developed and implemented [28]. Although specific guidelines are available to help clinicians in manging CVD risk in high risk groups [21], the appropriateness of these guidelines for women with a history of complicated pregnancy, including GDM, needs to be scrutinized [21].

There is a consistent positive association between GDM and the development of CVD in later life across studies, and this association seems to be independent of other CVD risk factors, including T2DM. Further, women with a history of GDM develop CVD at a relatively younger age. This knowledge should be considered more closely by health care providers and be transferred to practice with the aim of reducing CVD risk in this high-risk women group.

Declarations of interest

None.

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