**Is the history of miscarriage and/or stillbirth a risk factor for cardiovascular disease in women?**

Farnoosh Asgharvahedi, BSc, MSc

Faculty of Health, University of Technology Sydney, Australia

Email: Farnoosh.asgharvahedi@student.uts.edu

Leila Gholizadeh, BSc, MSc, PhD

Faculty of Health, University of Technology Sydney, Australia

Email: Leila.gholizadeh@uts.edu.au

Soraya Siabani, MD, PhD

School of Public Health, Kermanshah University of Medical Sciences, Iran

Email: ssiabani@kums.ac.ir

\*Corresponding Author

Leila Gholizadeh

Faculty of Health, University of Technology Sydney

15 Broadway (PO Box 123), NSW 2007, Australia,

T +61 2 95144814 E leila.gholizadeh@uts.edu.au

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# Abstract

Cardiovascular disease (CVD) remains the main cause of morbidity and mortality in women worldwide. Apart from the well-established risk factors, some adverse pregnancy outcomes have been found to be associated with increased risk of CVD in women. This study aims to review the literature on the risk of CVD in women with a history of pregnancy loss (miscarriage and/or stillbirth). Electronic databases including MEDLINE and CINAHL were searched for English language articles published from 2000 to July 2016. Following the application of study inclusion and exclusion criteria, 7 studies were selected for review. Women with history of miscarriage and/or stillbirth are more likely to develop coronary heart disease (CHD), but not stroke in their later life compared to women without these conditions. The risk is particularly greater in women with multiple miscarriages or stillbirths. Miscarriage and/or stillbirth should be considered as risk factor for developing CHD, but not stroke in women. Health professionals should be aware of the risk associated with miscarriage and stillbirth, and use maternal history to identify, refer, closely monitor, and engage these high risk women in healthy lifestyle and risk factor modification programs.

Key words: Cardiovascular disease, Coronary heart disease, Miscarriage, Stillbirth

# Background

Cardiovascular disease (CVD) is a leading cause of premature mortality in women (Wagner, Bhattacharya, Visser, Hannaford, & Bloemenkamp, 2015). CVD generally refers to any disease that affects the cardiovascular system, and includes but not limited to coronary heart disease (CHD) and cerebrovascular disease (stroke). Coronary heart disease/ ischemic heart disease/coronary artery disease refers to narrowing or blockage of coronary arteries, usually caused by atherosclerosis (Mosca et al., 2011). Although men and women share many common risk factors for CVD and exhibit overlap in clinical presentations, there exist important gender-based differences. Some risk factors are exclusive to women or affect women disproportionately. Diabetes, for example, is a greater risk factor for developing CVD in women than men and factors related to childbirth and menopause are unique to women. The incidence of CVD is similar in men and women after menopause (Mosca et al., 2011).

 There is emerging evidence linking adverse pregnancy outcomes to increased risk of CHD in women. The underlying mechanism of this association is unknown, however, several hypotheses have been proposed. One explanation is that duration of pregnancy in which women are exposed to high level of pregnancy estrogens is important for cardiovascular health (Kharazmi, Fallah, & Luoto, 2010), and a shorter duration of pregnancy in pregnancy loss predisposes women to CHD (Mahendru, Everett, McEniery, Wilkinson, & Lees, 2013). It is also possible the metabolic, hormonal, and haemostatic changes related to adverse pregnancy outcomes contribute to development of CHD in women (Kharazmi, Dossus, Rohrmann, & Kaaks, 2011), or the resulting vascular pathology may contribute to both poor placenta implantation, causing pregnancy loss and CHD in later life (Ranthe et al., 2013).

 The American Heart Association recognises adverse pregnancy outcomes, such as pre-eclampsia and gestation hypertension as early indicators of CVD risk in women, and advises that the current risk prediction tools, such as the Framingham Risk Score are likely to underestimate the risk of CHD in women. However, miscarriage and stillbirth, as adverse pregnancy outcomes, have not been explicitly stated in the American Heart Association’s guideline for prevention of heart disease in women. The aim of this review is to consolidate the evidence linking history of miscarriage and/or stillbirth to future CVD risk in women (Mosca et al., 2011).

 Miscarriage or spontaneous abortion is the most common complication in early pregnancy, and is defined as pregnancy loss before 20 weeks of pregnancy (Tulandi & Al-fozan, 2017). Miscarriage occurs in about 10-15% of all pregnancies (Sugiura-Ogasawara, 2015), and the main known risk factors include advanced maternal age, history of spontaneous pregnancy loss, and smoking (Tulandi & Al-fozan, 2017). Recurrent miscarriage refers to the loss of two or more pregnancies (Sugiura-Ogasawara, 2015), and it occurs in 0.5-3% of all fertile women (Tulandi & Al-fozan, 2017). Cause of recurrent miscarriage is multifactorial, yet, in about half of the cases, the underlying reason remains unexplained (Mahendru et al., 2013). Chromosomal defects are the main cause of an early miscarriage; however, in early or late recurrent miscarriages usually one or more maternal risk factors are involved. Many of these risk factors overlap with the CVD risk factors; for example, endothelial dysfunction and hypertension (Mahendru et al., 2013). Stillbirth is defined as death before complete separation from pregnancy products and mother, regardless of the duration of pregnancy. The threshold for defining stillbirth/ fatal death is gestational age≥ 22weeks, birth weight ≥500 grams, or crown-heel length≥25 cm. Stillbirth accounts for about half of all perinatal deaths (Calderon-Margalit et al., 2007).

# Methods

## Search strategy

The evidence linking miscarriage and stillbirth with future risk of CVD was accessed through electronic databases including MEDLINE and CINAHL. The search was limited to English language and to the literature published between January 2000 and July 2016. The search terms for the exposure included: ‘pregnancy loss\*’, ‘abortion\*’, ‘miscarriage\*, ‘fatal death\*’, ‘stillbirth\*’, ‘still birth\*, ‘stillborn’ and for the outcome included: ‘cardiovascular disease\*’, ‘coronary artery disease’, ‘myocardial infarction’, ‘coronary heart disease\*’, and ‘ischemic heart disease\*’. Only primary studies that investigated the link between miscarriage or stillbirth and risk of CVD in later life were included.

## Study selection

A total of 40 publications were retrieved from initial search; after limiting to English language and defined time period, 32 articles remained for screening. Review articles and duplications were removed, leaving 26 papers for further analysis. Eight further articles were removed in the process of title and abstract screening. The full texts of 18 studies were then reviewed for relevancy, resulting in the exclusion of 11 papers. In the end, 7 studies were included in the review (Figure 1). Of the reviewed studies, 4 studies were conducted in Europe (1 in Germany and 2 in Scotland, and 1 in Finland), 1study in Israeli, and 2 studies in the United States (Table 1).

# Results

The findings of this review are presented in two main categories: risk of CVD in women with history of miscarriage and risk of CVD in women with history of stillbirth.

## Risk of CVD in women with history of miscarriage

The findings of studies that examined the relationship between history of miscarriage and CVD consistently suggest that miscarriage (not abortion), particularly recurrent miscarriage is a risk factor for developing CHD, but not stroke in women. A retrospective population based study in Scotland (Smith, Pell, & Walsh, 2003) recruited 129290 women, who had their first live child between 1981 and 1985, to closely examine the risk of CHD in women with history of early miscarriage. The study found that women with history of early miscarriage, before the first live delivery, were more likely to have CHD events in later life. The risk increased with the number of early miscarriages. Women with 1-2 early mischarges were at increased risk of CHD (adjusted hazard ratio (HR) 1.48, 95% CI 1.09 to 2.02, p=0.01). The hazard ratio increased to 2.35 in women with 3 or more early miscarriages (95% CI 0.87 to 6.36, p=0.09). The increased risk was found to be independent of maternal age at the time of first birth, height, socioeconomic deprivation, history of essential hypertension, and adverse events during first pregnancy. There was no control for important confounders, such as smoking or diabetes. The study did not find association between termination of pregnancy through therapeutic interventions and future risk of CHD (Smith et al., 2003).

 Likewise, a prospective cross-sectional study, which focused on 3,937 Finnish women (aged 30-99) found that women with history of miscarriage had slightly, but not significant, increased risk for myocardial infarction (MI) in their later life (fully-adjusted odds ratio (OR)1.3, 95% CI 0.6 to 2.4). The results of sub group analysis showed significantly greater risk of MI in women within age group of 50-74 years (aged-adjusted OR 2.0 95% CI 0.9 to 4.0). The risk was particularly higher in women with recurrent miscarriages, with 40% increase in the risk per every episode of miscarriage (aged-adjusted OR per miscarriage 1.4 95% CI 1.1 to 1.8). The potential confounders were controlled for in this study (Kharazmi et al., 2010).

 A large population-based cohort study in Germany (Kharazmi et al., 2011) used a prospective approach to examine the relationship between miscarriage and future risk of MI. In this study, 11518 women within age range of aged 30-66 years, who had ever been pregnant and never had a history of MI or stroke, were followed up through regular questionnaires every 2-3 years for an average 10.8 years. Out of the participants, 25% experienced at least one miscarriage, 18% at least one abortion and 2% at least one stillbirth. During the follow-up period, 82 cases of MI and 112 cases of stroke were recorded for the cohort. Women who experienced miscarriage were more likely to smoke currently or in the past and had slightly higher waist to heap ratio. Women with recurrent miscarriage were more likely to have higher BMI and waist to heap ratio than other women. Similar to the Finish study, It was found that each miscarriage was associated with more than 40% increase in the risk of MI (age adjusted HR 1.42, 95% CI 1.14 to 1.78). The risk of MI was 9 times higher in women with recurrent miscarriage (>3) (age adjusted HR 8.90, 95% CI 3.18 to 24.90). When the analysis was limited to subgroup of women aged ≥ 49 and history of more than 3 miscarriages, the association between recurrent miscarriage and later MI remained unchanged (age adjusted HR= 9.07 95% CI 3.2 to 25.4). The study concluded that women with the history of miscarriage or recurrent miscarriage were at significantly greater risk of MI, and the risk remained significant after adjustment for other potential confounders (fully adjusted HR 5.06, 95% CI 1.29 to 20.29). There was found no significant association between abortion and later MI or between any type of pregnancy loss and stroke (Kharazmi et al., 2011).

 Another study (Parker et al., 2014) applied a retrospective approach to examine the relationship between miscarriage and later CVD events in 77701 post-menopausal women, with a mean follow up of 7.7 years. Out of the participants, 30.3% had a history of miscarriage, 2.2% stillbirth, and 2.2% both. The study found that women with a history of one miscarriage had greater risk for CHD, with the multivariable-adjusted OR of 1.19 (95% CI 1.08-1.32), however, the risk was not significantly different from women who had two or more miscarriages with the reported OR of 1.18 (95% CI 1.04 to 1.34). The study controlled for most potential confounders. Also, miscarriage was not associated with future ischemic stroke (Parker et al., 2014). The researchers hypothesised that metabolic, hormonal, and haemostatic changes associated with pregnancy loss were likely to contribute to the increased risk of CHD in affected women.

 The results of a Scottish cohort study (Wagner et al., 2015) with longer follow ups supported the findings of previous research. This prospective study recruited 60105 women and followed them up for 17 years. Out of the participants, 15.67% experienced non-consecutive miscarriage(s), 1.56% had two consecutive miscarriages, 0.28% had three or more consecutive miscarriages and 82.49% had no miscarriage. The study excluded women with pre-existing morbidity, such as type one diabetes mellitus, hypertension, and kidney disease, the effects other important confounders were controlled for. The study found that women who had two consecutive miscarriages had 1.75 times higher risk for developing CHD compared to women with no history of miscarriage (95% CI 1.22-2.52). The risk of CHD tripled (HR 3.18 (95% CI 1.49 to 6.80) in women with three or more consecutive miscarriages compared to women with no history of miscarriage. Similar findings were observed when the data were analysed irrespective of whether the miscarriage occurred consecutively or not. Therefore, the study concluded that there was significantly positive association between number of miscarriages and risk of CHD, irrespective of whether consecutive or not (Wagner et al., 2015).

 A more recent study (Parikh et al., 2016) followed up 93676 postmenopausal women. Women with missing reproductive and CHD risk factor information, those with no follow up information, and women with predominant or unknown history were excluded, leaving 72982 women for further investigation. An age-adjusted Cox proportional hazards analysis revealed that the risk of CHD was greater in women with single miscarriage (HR 1.13, 95% CI 1.05 to 1.22), in women with 2 to 4 miscarriages (HR 1.28, 95% CI 1.16 to 1.41), and in women with more than 5 miscarriages (HR 1.55, 95% CI 1.15 to 2.09). The associated risk remained significant after adjusting for established CHD risk factors. It should be noted this study considered postmenopausal CHD events only (Parikh et al., 2016).

## Risk of CVD in women with history of stillbirth

Studies that examined the associations between stillbirth and the risk of future CVD consistently reported significant positive associations between stillbirth and the risk of CVD in future. A population based cohort study focused on women who had at least two deliveries between 1964 and 1976 in Israel with median follow ups of 36.5 years. Data were gathered through linkage with the Israeli population registry. The death rates were compared between 595 women with a history of stillbirth and 24523 women who had only live births. The rate of all-cause death was found to be 13.1% vs 6.2% in women with and without history of stillbirth respectively (HR 2.08, 95% CI 1.65 to 2.61). The adjusted hazard ratio of death from CHD was 2.00 (95% CI 1.02 to 3.93), all circulatory HR 1.70 (95% CI 1.02 to 2.84), and renal disease HR 4.70 (95% CI 1.47 to 15.0). Women of North African origin were found to be at particularly higher all-cause mortality risk with adjusted HR of 2.47 (95% CI 1.69-3.63). The association between stillbirth and later death did not change when the analyses were adjusted for history of gestational diabetes. The study suggested that stillbirth should be considered as an early indicator of premature death in fertile women. The study concluded that the relationship between stillbirth and later death is not causal but rather maternal metabolic disorders underlie both stillbirth and later CVD death (Calderon-Margalit et al., 2007).

 Similarly, Kharazmi et al. (2011) found that age-adjusted HR of MI increased by 2.65 in women with a history of stillbirth (95% CI 1.37 to 5.12). Women with stillbirth were more likely to be older, less educated, physically less active, diabetic, and have hyperlipidaemia and hypertension in compare with women without the condition. The association between stillbirth and later MI remained significant after adjusting for potential confounders (HR 2.32, 95% CI 1.2 to 4.9) (Kharazmi et al., 2011). Consistent with these findings, Parker et al. (2014) reported that women with 1 or more stillbirths in compare with women without the history of stillbirth had greater multivariable-adjusted odds ratio of CHD (OR 1.27, 95% CI 1.07 to 1.51). As the interactions between stillbirth and diabetes, hypertension, lipid levels, and ethnicity were not significant; these variables were not included in the final multivariable model. Similar to Kharazmi et al.’s study (2011), women with the history of stillbirth were more likely to be older in this study (Parker et al., 2014). More recently, Parikh et al. (2016) reported that in compare to women without the history of stillbirth, women with the history of one stillbirth had an increased risk of CHD with the aged-adjusted Cox proportional hazard of 1.24 (95% CI 1.07 to 1.44). After adjusting for the well-established CHD and other reproductive and pregnancy risk factors, the study concluded that stillbirth was an independent risk factor for CHD in later life (Parikh et al., 2016).

# Discussion

The results of this review suggest that women with a history of miscarriage compared to women without miscarriage are at increased risk for developing CHD in later life. The risk is particularly greater in women with recurrent miscarriages (Kharazmi et al., 2011; Kharazmi et al., 2010; Oliver-Williams, Heydon, Smith, & Wood, 2013), irrespective of being consecutive or not (Wagner et al., 2015). Early miscarriage (Smith et al., 2003) and the number of miscarriages have been found to strengthen the associations between miscarriage and future CHD . No evidence was found regarding any association between induced abortion and risk of CHD (Kharazmi et al., 2011; Smith et al., 2003). The risk of CHD and premature death is consistently higher in women with history of stillbirth (Kharazmi et al., 2011; Kharazmi et al., 2010; Parikh et al., 2016; Parker et al., 2014), and this risk seems to be independent of the well-established CHD risk factors . However, no association was found between miscarriage and/or stillbirth and future stroke (Parker et al., 2014).

 Although the relationship between pregnancy loss (miscarriage and still birth) and CHD is established, there remains the need for further research to determine the extent and type of (Smith et al., 2003; Wagner et al., 2015) cardiovascular complications associated with pregnancy loss. Also, it is not yet clear if women with history of both miscarriage and stillbirth are at greater risk of developing CHD compared to women with history of only miscarriage or stillbirth. Further research is needed to examine racial differences in the association between miscarriage or stillbirth and future CHD. The association between stillbirth and all-cause mortality was found to be greater in African women in one study (Calderon-Margalit et al., 2007).

 In addition, the underlying pathophysiological mechanisms linking pregnancy loss to development of CHD are yet to be elucidated (Mahendru et al., 2013). It seems that miscarriage and stillbirth affect the risk of future CHD both synergistically with other risk factors and independently. Some genetic or epigenetic features seem to predispose women to both pregnancy loss and CHD. To test this hypothesis, Smith et al. (2011) studied 74730 women with first birth to find out the association between their experience of pregnancy losses before the first live birth and family history of CVD. It was found that women with history of two pregnancy loss before first live delivery 25% higher risk of having family history of CHD (95% CI 1.04-1.49) and the risk was even greater (56%) in women with three or more miscarriages before first live birth (95% CI 1.14-2.15). However, this study could not establish a significant relationship between elective abortion before first live delivery and family history of CVD. The study suggested that there are shared patho-physiological trails and genetic susceptibilities between spontaneous miscarriage and CHD (Smith, Wood, Pell, & Hattie, 2011).

 Regardless of the underlying pathological mechanisms, the risk of CHD is higher in women with a history of pregnancy loss. Health professionals and women need to be aware of this risk and identify, appropriately assess, and monitor women with history miscarriage and/or still birth for future CHD risk. The reproductive risk factors could be easily identified by taking a medical history and therefore constitute a simple, non-invasive, and inexpensive risk stratification tool. These reproductive factors often precede the onset of established CHD risk factors in younger women and could thus indicate the need for early risk modification. Consideration of history of adverse pregnancy outcomes in CHD risk stratification, either alone or in concert with other established risk factors, may enhance clinicians’ ability to better risk stratify young women in a simple and cost-effective way. The usefulness of inclusion of pregnancy loss history, as an independent risk factor, in the current CHD risk prediction tools for women needs to be further studied. Improved CHD risk prediction tools could enable better risk stratification and identification of high risk women, who could benefit from timely supportive interventions.

 Complications during pregnancy in the form of miscarriage or stillbirth could be one of the earliest clinical indicators of developing CHD in future life. Early identification of these high risk women provides a window of opportunity for timely intervention to prevent CHD or minimise the complications.

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