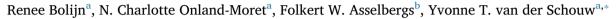
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Reproductive factors in relation to heart failure in women: A systematic review



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ABSTRACT

Background: The biological mechanisms underlying the sex-related differences in risk of heart failure are still not well understood. The aim of this review was to provide an overview of the current evidence on the association between reproductive factors and risk of heart failure in women.

Methods: A systematic review of the literature was conducted. PubMed and Embase databases were searched for publications on the following reproductive factors as potential risk factors for heart failure in women: age at menarche, duration and frequency of the menstrual cycle, reproductive lifespan, use of contraception, polycystic ovarian syndrome (PCOS), pregnancy characteristics (e.g. parity), pregnancy complications (e.g. preeclampsia), induced abortion, history of breastfeeding, fertility status, use of assisted reproductive methods, hysterectomy, age at menopause, and use of hormone replacement therapy (HRT).

Results: Twenty-one studies were eligible for inclusion. Hypertensive pregnancy disorders, preterm delivery or small-for-gestational-age (SGA) infants, shorter reproductive duration, and early menopause were risk factors for heart failure in women. It was suggested that PCOS, fertility therapy, gestational diabetes, and age at first pregnancy were not related to risk of heart failure, but a potential relation cannot be fully excluded as most studies were not of sufficient quality. Conflicting results were found for the associations between risk of heart failure and hysterectomy, gravidity and parity, and HRT.

Conclusion: Although some reproductive factors were considered risk factors for heart failure in women, the results were mostly conflicting or inconclusive. Further research is needed to confirm and expand the current evidence on the association between reproductive factors and risk of heart failure.

1. Introduction

In many countries, cardiovascular diseases (CVD) represent the largest burden of disease [1], and it is expected that the burden of CVD will further increase in the upcoming years, with coronary heart disease (CHD) and stroke as the major drivers [2]. In 2010, it was estimated that approximately one third of all deaths globally was due to CVD [1]. In Europe, these numbers are even more alarming, with an estimated 45% of deaths caused by CVD in 2015 [3].

It is well known that major differences exist in CVD between men and women with regard to epidemiology, clinical presentation, and prognosis. For example, the incidence of CVD in men steadily increases from their mid–30 s onwards, whereas CVD is hardly seen in premenopausal women [4]. However, after menopause, which usually occurs around the age of 51 years [5], CVD incidence and mortality in women increase progressively [4,6]. Furthermore, diabetes and hypertension are more prominent risk factors for CVD in women than in men [4]. Next to these shared risk factors, reproductive history and gynaecological disorders, such as polycystic ovary syndrome (PCOS), have been recognized as additional cardiovascular risk factors for women [7]. For stroke, it is mostly the prevalence of the various symptoms and signs which differ between men and women, but for CHD, its development varies significantly by sex [8]. However, treatment guidelines for stroke and CHD in women and men are currently the same [8]. Also, CHD mortality in women is higher compared to men [9], while the opposite is true for stroke [10].

In CVD research, much emphasis has been on stroke and myocardial infarction (MI), although a substantial proportion of CVD initially presents as heart failure [11], especially in women [11,12]. Heart failure is a major increasing health problem worldwide [13,14], with currently a prevalence of about 1–2% [15]. Whereas mortality rates of CHD and other CVDs have declined over the past decades, mortality

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rates of heart failure have been increasing [13]. Furthermore, the overall survival has improved for heart failure patients, which resulted in a higher average age at death and lower age-adjusted death rates [13], but the 5-year mortality rate is still 50% [16]. As heart failure is usually the endpoint for many CVD, it has a significant role in the global burden of disease [17].

Sex differences have also been observed for heart failure. For example, women with heart failure tend to have a better prognosis compared to men with heart failure, although it depends on the underlying aetiology [17]. Furthermore, hypertension is a more common cause for heart failure in women than it is in men, whereas MI is a more common cause for heart failure in men compared to women [18]. More female than male heart failure patients present with preserved left ventricular function [18,19]. Also, men with heart failure generally experience a higher quality of life than women with heart failure [20], due to the higher frequency of hospitalizations and the higher burden of symptoms in women [21].

The biological mechanisms underlying the sex-related differences in heart failure and other CVD are still not well understood. Extensive research has been performed on the relation between various womenspecific risk factors (or reproductive factors) and CHD or stroke in an attempt to explain these sex-related differences. Several reviews and meta-analyses showed that age at menarche [22], hormonal contraceptives [23], hypertensive pregnancy disorders [24,25], gestational diabetes [25], miscarriage [26], history of preterm delivery [25,27], and age at menopause [28] were associated with any CVD morbidity or mortality, whereas hormone replacement therapy was not [29]. Heart failure was not included in these reviews and meta-analyses. The aim of this review is, therefore, to provide an overview of the current evidence on the association between reproductive factors and risk of heart failure in women. Furthermore, challenges and recommendations for future research will be discussed.

2. Methods

2.1. Eligibility criteria

Studies were considered eligible for this review if they presented original research on women examining the association of any of the following reproductive factors: age at menarche, duration and frequency of the menstrual cycle, reproductive lifespan, use of contraceptive methods, PCOS, pregnancy characteristics (e.g. gravidity, parity interpregnancy interval, maternal age), pregnancy complications (e.g. gestational diabetes, preeclampsia, miscarriages), induced abortion, history of breastfeeding, fertility status, assisted reproductive methods, hysterectomy, age at menopause, menopausal status, and use of hormone replacement therapy, with risk of developing heart failure. The study population had to consist of women over the age of 18 years and at least a part of the study population had to consist of women without a known history of cardiovascular disease at the beginning of the study. Animal studies and studies published in a language other than English were excluded. Guidelines, reviews, meta-analyses, case reports, case series, editorials and comments were also excluded. Conference abstracts were included, unless the study was covered by a published article. As we were interested in the long term effects of reproductive factors on potential heart failure, studies examining heart failure during or within a few months after pregnancy ('peripartum') were not included in this review. There was no restriction imposed on year of publication.

2.2. Data sources

The databases of PubMed and Embase were systematically searched from inception to 24 June 2016 for studies examining potential associations between the abovementioned reproductive factors and risk of heart failure in women. Medical Subject Heading (MeSH) terms and similar Emtree terms for all reproductive factors ("reproductive history", "menarche", "menstrual cycle", "contraceptive agents, female", "polycystic ovary syndrome", "pregnancy complications", "maternal age", "abortion, induced", "breast feeding", "parity", "fertility agents", "reproductive techniques", "hysterectomy", "menopause", and "hormone replacement therapy") were combined with those for heart failure ("heart failure"). Furthermore, titles and abstracts were searched with similar terms for all reproductive factors and heart failure. The database searches were restricted to women, humans, and aetiological studies, and studies examining heart failure in women during or within a few months after pregnancy were excluded using the term 'peripartum'. The search strings can be found in Appendix A.

2.3. Study selection

After removal of duplicates, titles and abstracts of all publications retrieved from PubMed and Embase were screened. All potential relevant publications were assessed for eligibility by applying the eligibility criteria to the selected full-text articles. The snowball method was performed by hand-searching the references and related articles of the articles selected by the electronical database search to identify any potential additional relevant publications.

2.4. Data extraction

The data extracted from each selected study included information about the study population (e.g. size, mean age), study design and follow-up (if applicable), determinants (i.e. the studied reproductive factors), outcome, and measures of association (i.e. odds ratios, hazard ratios etc.), including 95% confidence intervals and the factors adjusted for.

2.5. Quality assessment

The methodological quality of the eligible studies was assessed using the study quality assessment tools from the National Heart, Lung and Blood Institute (NHLBI), National Institute of Health (NIH), USA [30]. These tools comprise eight to fourteen criteria (depending on the study design) of which the reviewer has to state if they were met or not, or were either not reported, could not be determined or were not applicable. The reviewer has to provide the study with a rate of 'good', 'fair', or 'poor', based on own judgement using the criteria.

3. Results

3.1. Search results

The initial electronic database search resulted in 1648 potentially relevant publications; 981 from PubMed and 667 from Embase. After removal of duplicates, 1490 publications were analysed by screening titles and abstracts. Of the screened publications, 70 were assessed for eligibility by full text reading, of which 19 were included in this review. The other records were excluded for various reasons: fourteen articles were reviews, comments or editorials, the determinant and/or outcome of twelve studies were not relevant for this review, nine studies only examined cardiovascular diseases as a composite outcome (including heart failure), seven publications were conference abstracts of which the study was also covered by a published article, seven articles were not available, and two studies were excluded for other reasons. Using the snowball method, two additional publications were found eligible. The final number of studies included in this review was 21. The flow diagram of the study selection is shown in Fig. 1.

Table 1 presents the characteristics of the eligible studies examining the association between reproductive factors and risk of heart failure in women, categorized by type or category of reproductive factor. One study was a randomized controlled trial. The other studies were Download English Version:

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