Number of Pregnancies and Risk of Atrial Fibrillation

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ABSTRACT: Pregnancy is associated with major structural and hemodynamic changes in the cardiovascular system that predispose women to an increased risk of atrial fibrillation. While these changes generally resolve after parturition, the impact of subsequent pregnancies on the risk of atrial fibrillation is unknown. We searched through PubMed for studies that have investigated the impact of multiparity on the risk of atrial fibrillation. The following Medical Subject Headings terms were used: ([repeated pregnancies] OR parity) AND ([Atrial fibrillation] OR AF). Studies with complete data were included in the current study. Out of 135 studies identified through the prespecified criteria, we selected 2 studies with relevant data. Increasing number of pregnancies was associated with an increased risk of atrial fibrillation in a dose-response relationship. Our systematic review suggests that multiparity is associated with an increased risk of atrial fibrillation. More studies are warranted to elucidate the association between repeated pregnancies and atrial fibrillation. (Curr Probl Cardiol 2021;46:100697.)

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Introduction

Atrial fibrillation (AF) is a common cardiac dysrhythmia in the United States (US) that is associated with substantial morbidity and mortality. However, its true prevalence is unknown and many cases remain undiagnosed. It is estimated that between 2.7 and 6.1 million people in the US had AF in 2010 and that the prevalence is projected to double by 2030.[1] Moreover, AF was associated with 154,816 deaths in the US in 2016. Interestingly, while men have a higher prevalence of AF than women, women tend to be more symptomatic and exhibit poor response to therapy including a higher mortality rate.[2,3]

Differences in the prevalence of AF in men and women may partly be explained by gender differences in traditional risk factors for AF. For example, women are more likely to have hypertension, diabetes, valvular disease, and thyroid disease while men are more likely to have idiopathic AF and coronary artery disease.[4] Moreover, women have unique risk factors that predispose them to increased risk of AF. Notably, pregnancy is associated with structural and physiologic changes that affect multiple pathways for cardiovascular disease.[5,6] Indeed, a large retrospective cohort study (n = 1,332,062) based on data from the Swedish population registries showed a J-shaped association between parity and cardiovascular disease with the lowest risk among women with 2 births and the highest risk among women with ≥5 births.[7]

Interestingly, the aforementioned structural and physiologic changes in pregnancy also contribute to the increased risk of AF in women and this risk may be further elevated with repeated pregnancies.[8,9] However, very few studies have investigated this association and the impact of multiple pregnancies on AF is yet to be elucidated. The current study aims to explore the association between number of pregnancies and AF through a systematic review of the existing literature.

Methods

We used PubMed to conduct a systematic review of studies that have investigated the association between multiple pregnancies and atrial fibrillation. The following Medical Subject Headings were used: ([repeated pregnancies] OR parity) AND ([atrial fibrillation] OR AF). We sought for additional studies through a manual search of references in studies accrued after applying the above search criteria. This study was conducted in concordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[10] and the Preferred Reporting Items for

Systematic Reviews and Meta-Analysis (PRISMA) statements.[11] All human studies with data on the association between number of pregnancies and AF were included in the current systematic review.

Results

Using the aforementioned search criteria, we identified 135 studies out of which we selected 2 studies with relevant data for the current study.

Number of pregnancies and atrial fibrillation

The first study that we identified was a case-control study (cases = 118; Controls = 591) by Scantlebury et al[12] using data from the Kentucky Health registry among women who were 40 years or older. This study was conducted from December 2009 to June 2011. In results adjusted for age, any parity was associated with a 2.4-fold increased odds of AF. In results categorized by number of pregnancies, there was suggestion of a J-shaped relationship between parity and AF with a nadir at 3 pregnancies. However, the results for the different parity categories were not significantly different.

The second study was a large prospective cohort study (n = 34,639) by Wong et al[13] using data from the Women's Health Study. This study had a median follow-up of 20.5 years and participants had a baseline median age of 52.9 years. To minimize confounding, Wong et al excluded women with self-reported AF, cardiovascular disease, or unknown number of pregnancies at baseline. In results adjusted for age, smoking, alcohol use, height, race, education, income, exercise, marital status, hormone replacement therapy, body mass index, diabetes, hypertension, hypercholesterolemia, history of pregnancies <6 months, duration of oral contraceptive use, age of menarche, age of menopause, surgical menopause, and hysterectomy, Wong et al showed a linear dose-response association between AF events and increasing number of pregnancies (0 pregnancy: reference; 1 pregnancy: Hazards Ratio [HR] = 1.17; 95% Confidence Interval [CI]: 0.89-1.55); 2-3 pregnancies: HR = 1.21 (95% CI: 0.97-1.52); 4-5 pregnancies: HR = 1.37 (95% CI: 1.08-1.74); 6+ pregnancies: HR = 1.49 (95% CI: 1.12-1.98); $P_{\text{for trend}} = 0.002$). The results did not change in models further adjusted for additional covariates that could potentially influence the development of AF.

Discussion

There is paucity of data on the association between number of pregnancies and AF. Our systematic review, based on the few studies that we

identified, indicates that multiparity may be associated with an increased risk of AF in women. Moreover, this association appears to have a dose-response relationship where increased number of pregnancies are associated with an increased risk of AF.

To our knowledge, this is the first systematic review of studies that have investigated the association between multiparity and AF. Pregnancy is associated with multiple hormonal, physiologic, and structural changes that have major effects on the cardiovascular system and possibly the risk of AF.

In response to increasing demands of the growing embryo, there is an increase in blood volume, red blood cell mass, heart rate and cardiac output.[6,14] Activation of the renin-angiotensin-aldosterone system has been shown to be responsible for the increased plasma volume in pregnancy while elevated levels of erythropoietin in pregnancy are thought to be the cause for the increased red blood cell mass.[15,16] To accommodate for the increased circulatory volume, vasodilatory hormones, specifically estrogen, progesterone, and relaxin, are elevated in early pregnancy leading to a net decrease in total peripheral resistance and an increase in capacitance of the cardiovascular system.[15,17] Consequently, there is a decrease in diastolic and mean atrial blood pressure in pregnancy compared to the prepregnancy state.[6]

Due to the increased hemodynamic demand, pregnancy is also associated with significant structural changes of the myocardium. Robson et al[18] showed that pregnancy is associated with a 28% increase in left ventricular (LV) thickness and a 52% increase in LV mass. A recent study by Ducas et al[19] showed that pregnancy is associated with a significant increase in both the right and left ventricular mass. This study also found that pregnancy is associated with a significant increase in LV end diastolic diameter and LV end diastolic volume with a concomitant doubling in cardiac output. Through an animal model study, Umar et al[20] showed that the cardiac hypertrophic state in pregnancy is associated with increased vascular endothelial growth factor and angiogenesis in the myocardium that is reversed after parturition.

However, while the pregnancy-induced myocardial changes have been shown to resolve after parturition in normal pregnancy, there are very few studies that have investigated the impact of multiparity on the myocardium. It is possible that subsequent pregnancies may result in permanent changes in the cardiovascular system. Indeed, multiparity is associated with increased venous tone, decreased compliance and increased response to phenylephrine and acute stress.[21] In fact, it has been demonstrated that multiple pregnancies are associated with an

increased risk of coronary artery disease.[22] The current review shows that multiparity is also associated with an increased risk of atrial fibrillation.

We acknowledge 2 main limitation for the current study. First, we identified only 2 studies that have investigated the association between multiparity and atrial fibrillation which limits the generalizability of the current study. Second, the 2 studies were conducted in the United States and majority of the participants were white which further limits the generalizability of their findings. Nevertheless, the current review provides a unique view of multiparity as a risk modifier for atrial fibrillation among women. More studies are warranted to investigate this association in diverse populations.

Conclusion

Our systematic review suggests that multiparity is associated with an increased risk of atrial fibrillation. More studies need to be conducted to further elucidate the association between number of pregnancies and atrial fibrillation in diverse populations and settings.

Author contributions

Study concept: NK. Study design: JK, SM. Data acquisition: JK, SM, DH, NK, AK. Drafting the manuscript: JK, SM, DH, NK, AK. Critical revision of manuscript for important intellectual content: All authors. Final manuscript approval: All authors.

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