Increased parity is independently associated with risk of cardiovascular disease (CVD) in large observational studies. Although CVD is a strong risk factor for the development of atrial fibrillation (AF), little is known about the relationship between parity and AF risk. To address these gaps in knowledge, and given the significant impact AF has in women, we sought to examine the relationship between parity and AF in a large cohort of women free of CVD and AF at baseline within the WHS (Women's Health Study).

WHS began as a randomized trial examining the use of aspirin versus placebo for the primary prevention of CVD and cancer. The study enrolled 39,876 women aged ≥45 years without CVD or any major illness. Development of prespecified health outcomes, and updated demographic, lifestyle, and CVD risk factor information were captured in annual questionnaires. The randomized trial was completed in March 2004, and subjects were invited to participate in observational follow-up. Women reported their number of pregnancies lasting at least 6 months in duration at baseline and incident AF events beginning at 48 months and annually thereafter. Medical records were sought for all self-reported incident AF cases, and events were adjudicated by a committee of cardiologists. Only AF events confirmed by medical record review were included in the analysis.

Patients who self-reported AF (n=876), CVD (n=14), or an unknown number of pregnancies at baseline (n=137) were excluded. We also excluded 4,210 women who did not participate in observational follow-up because AF could not be reliably confirmed. The study population thus consisted of 34,639 women. All participants provided written informed consent, and the study was approved by Brigham and Women's Hospital institutional review board.

The number of pregnancies ≥6 months was grouped into 5 categories (0 [reference], 1, 2–3, 4–5, ≥6) adapted from Ness et al. Multivariable, time-updated, Cox proportional-hazards models were used to estimate the association between number of pregnancies and incident AF. Tests for linear trend were performed by assigning the median value to each pregnancy category and modeling this as a continuous variable in separate Cox models. All models were constructed without imputation for missing data. Person-time was calculated from return of the baseline questionnaire to the date of incident AF, death, loss to follow-up, or December 31, 2014, whichever occurred first.

Median baseline age was 52.9 years (interquartile range, 48.9–58.8), and median number of pregnancies was 2 (interquartile range, 2–3). During a median follow-up of 20.5 years, 1,532 incident AF cases occurred. The Table summarizes multivariable-adjusted hazard ratios and 95% confidence intervals for incident AF according to the number of pregnancies. After adjusting for age, there was a linear increase in the hazard ratio for incident AF across increasing parity categories (P-trend=0.004). This relationship was strengthened after controlling for body mass index, diabetes mellitus, other AF and CVD risk factors.

Jorge A. Wong, MD, MPH
Kathryn M. Rexrode, MD, MPH
Roopinder K. Sandhu, MD, MPH
David Conen, MD, MPH
Christine M. Albert, MD, MPH

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Correspondence to: Jorge A. Wong, MD, MPH, DBCVSRI Room C3-13C, 237 Barton Street East, Hamilton, ONT L8L 2X2, Canada. E-mail jorge.wong@phri.ca

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reproductive factors and markers of socioeconomic status, both at baseline and in time-updated models (Table, models 1–3). Additional adjustment for interim CVD events (model 4) did not alter the results.

Our study is the first to report an independent association between parity and AF risk. In comparison with nulliparous women, increasing number of pregnancies was associated with a linear increase in the risk of incident AF after adjustment for multiple confounders including shared risk factors such as obesity, hypertension, and diabetes mellitus, and reproductive risk factors and socioeconomic markers, as well. CVD events during follow-up were not important intermediaries in the relationship between parity and AF. We hypothesize that the association between parity and AF may be because of repeated exposure to physiological, metabolic, and hormonal factors during pregnancy. Pregnancy leads to physiological cardiac hypertrophy that, although reversible, may take >1 year to resolve in multiparous women.4 Pregnancy can lead to large fluctuations in reproductive hormones, renin-angiotensin-aldosterone system activation, inflammation, and endothelial dysfunction.5 Multiple activations of these pathways, also implicated in AF pathogenesis, via repeated pregnancies may increase AF risk.

Our study has several limitations. Our results may not be generalizable to women of all races or ethnicities because our study cohort was primarily of European descent and included participants in a randomized trial. Number of pregnancies and AF were both ascertained by self-report and may be subject to ascertainment biases. There is also the potential for misclassification in our exposure that, if nondifferential, would bias our results toward the null. However, self-reported number of pregnancies is highly reproducible.1 Despite our attempts to thoroughly control for multiple confounders, including socioeconomic status, we cannot exclude the possibility that residual confounding could have contributed, in part, to our findings.

In conclusion, in this large prospective cohort of initially healthy women, increasing number of pregnancies was associated with subsequent elevations in AF risk. Repeated exposure to metabolic, physiological, and hormonal changes during pregnancy may predispose to AF in later life and requires further investigation.

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<table>
<thead>
<tr>
<th>Table. Multivariable Adjusted Hazard Ratios and 95% Confidence Intervals for Incident Atrial Fibrillation According to Baseline Number of Pregnancies Categories</th>
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</thead>
<tbody>
<tr>
<td><strong>No. of Pregnancies</strong></td>
</tr>
<tr>
<td>Atrial fibrillation cases, n</td>
</tr>
<tr>
<td>Patient years</td>
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<tr>
<td>Atrial fibrillation incidence rate*</td>
</tr>
<tr>
<td>Age-adjusted</td>
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<tr>
<td>Model 1†</td>
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<td>Model 2‡</td>
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<td>Model 3§</td>
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<td>Model 4‖</td>
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</table>

Covariates were time updated as necessary. Data represent hazard ratios and 95% confidence intervals. N/A indicates not available.

*Per 1000 person-years.
†Model 1: Also adjusted for smoking status, alcohol use, height, race, education, income, exercise, marital status, and hormone replacement therapy use.
‡Model 2: Also adjusted for body mass index (kg/m²), history of diabetes mellitus, hypertension, hypercholesterolemia, history of pregnancies <6 mo, duration of oral contraceptive use, age of menarche, age of menopause, surgical menopause, and prior hysterectomy.
§Model 3: Also adjusted for the following time-updated covariates: smoking status, alcohol use, exercise, use of hormone replacement therapy, body mass index, history of hypertension, diabetes mellitus, and hypercholesterolemia.
‖Model 4: Also adjusted for cardiovascular events occurring prior to atrial fibrillation onset. Cardiovascular disease events included myocardial infarction, stroke, and coronary revascularization.
None.

From Population Health Research Institute, McMaster University, Hamilton, ON, Canada (J.A.W., D.C.); Division of Preventive Medicine (J.A.W., K.M.R., C.M.A.) and Cardiovascular Division (C.M.A.), Department of Medicine, Brigham and Women’s Hospital and Harvard Medical School, Boston, MA; Mazankowski Alberta Heart Institute, University of Alberta, Edmonton, Canada (R.K.S.); and Division of Internal Medicine, Department of Medicine, University Hospital, Basel, Switzerland (D.C.).

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Jorge A. Wong, Kathryn M. Rexrode, Roopinder K. Sandhu, David Conen and Christine M. Albert

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