Impact of a History of Hypertension in Pregnancy on Later Diagnosis of Atrial Fibrillation

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Background—Atrial fibrillation/flutter (AF) produces significant morbidity in women and is typically attributed to cardiac remodeling from multiple causes, particularly hypertension. Hypertensive pregnancy disorders (HPDs) are associated with future hypertension and adverse cardiac remodeling. We evaluated whether women with AF were more likely to have experienced a HPD compared with those without.

Methods and Results—A nested case–control study was conducted within a cohort of 7566 women who had a live or stillbirth delivery in Olmsted County, Minnesota between 1976 and 1982. AF cases were matched (1:1) to controls based on date of birth, age at first pregnancy, and parity. AF and pregnancy history were confirmed by chart review. We identified 105 AF cases: mean age 57±8 (mean±SD) years, (controls 56±8 years), 32±8 years (controls 31±8 years) after the first pregnancy. Cases were more likely to have obesity during childbearing years, and hypertension, diabetes mellitus, dyslipidemia, coronary disease, valvular disease, and heart failure at the time of AF diagnosis. Cases were more likely to have a history of HPDs, compared with controls: 28/105 (26.7%) cases versus 12/105 (11.4%) controls, odds ratio: 2.60 (95% confidence interval, 1.21–6.04). After adjustment for hypertension and obesity, the association was attenuated and no longer statistically significant; odds ratio (95% confidence interval, 2.12 (0.92–5.23).

Conclusions—Women with AF are more likely to have had a HPD, a relationship at least partially mediated by associated obesity and hypertension. Given the high morbidity of AF, studies evaluating the benefit of screening for and management of cardiovascular risk factors in women with a history of HPD should be performed. (*J Am Heart Assoc*. 2018;7:e007584. DOI: 10.1161/JAHA.117.007584.)

Key Words: atrial fibrillation • hypertension • obesity • preeclampsia/pregnancy • women

Atrial fibrillation/flutter (AF) is a major public health problem, with increasing prevalence and burgeoning health costs.[1,2] It is associated with significant morbidity and mortality, especially in women.[3] The most commonly observed risk factor for AF is hypertension.[2]

Women with a history of a hypertensive pregnancy disorder (HPD) are ≈4 times more likely to develop hypertension later in life,[4,5] and also develop hypertension ≈10 years earlier than women who have had normotensive pregnancies.[6]

Hypertension in pregnancy is common, occurring in up to 10% of pregnancies worldwide,[7] and may be increasing in prevalence.[8] The HPDs include 4 conditions: gestational hypertension, preeclampsia, chronic hypertension in pregnancy, and chronic hypertension with superimposed preeclampsia. Eclampsia is a severe form of preeclampsia, in which women develop seizures.[9]

Acute myocardial manifestations of the HPDs include concentric remodeling, left ventricular hypertrophy, and

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Clinical Perspective

What Is New?

- It is unknown whether hypertensive pregnancy disorders (HPDs) have an impact on the prevalence of atrial fibrillation/flutter (AF) later in life.
- This study demonstrates that women with a history of HPD are at increased risk for the development of AF later in life.
- This association is at least partially mediated by associated obesity and development of chronic hypertension following HPD.

What Are the Clinical Implications?

- The knowledge of the increased risk for AF in women with HPDs presents an opportunity for targeted surveillance for AF in these women, leading to earlier diagnosis and potentially a reduction in its morbidity.
- Strict attention to lifestyle modification and careful monitoring for and treatment of hypertension in women with a history of HPD may lead to a reduction in AF burden.

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diastolic dysfunction,[10] which results in left atrial enlargement,[11] accompanied by increased atrial natriuretic peptide levels.[12] Over the long term, women with a history of HPD have higher left ventricular mass and higher prevalence (odds ratio: 1.4) of left ventricular hypertrophy compared with women with normotensive pregnancies,[13] as well as a higher likelihood of an abnormal index of myocardial performance.[14]

AF is a common and important consequence of left ventricular diastolic dysfunction.[15] The emerging epidemic of obesity and metabolic syndrome may play a role in the increased prevalence seen in both HPDs and AF,[1,8] and there are multiple other potential mechanisms that could connect these 2 conditions. Despite this, a relationship between the disorders has not been examined. Our hypothesis was that women with HPDs would have an increased risk for developing AF later in life. We therefore conducted a case–control study to determine whether women with AF were more likely to have a history of a HPD compared with those without AF. Additionally, we explored whether any observed relationship between HPD and AF is mediated by a history of hypertension or obesity.

Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request. Methods for abstracting data and analytic methods are stated below and can be used to reproduce this study in other cohorts.

Study Setting

We conducted a case–control study using the Rochester Epidemiology Project (REP). This records linkage system captures healthcare information from all healthcare providers in Olmsted County, Minnesota, from 1966 to the present, providing health information on virtually the entire population of the county. Full details of the REP have been published previously.[16] Approximately 96% of Olmsted County residents have provided authorization for use of their medical records in research; thus, the requirement for informed consent was waived. This study was approved by the Mayo Clinic Institutional Review Board (protocol # 10-005198) and the Olmsted Medical Center Institutional Review Board (protocol # 046-OMC-10).

Study Population

The REP was used to identify cases and controls from a cohort of 7566 women who gave birth to a live or stillborn infant in Olmsted County between 1976 and 1982. Potential cases were identified as women from the birth cohort who provided research authorization, had a diagnostic code for AF (Table S1) before June 30, 2012, and had sufficient pregnancy information recorded to apply the algorithm for the definition of HPD for at least 1 pregnancy (Table S2). The medical records of the AF cases were manually reviewed for confirmation of the diagnosis, and the date of the AF diagnosis was defined as the index date. Women who were excluded from the case group because chart review showed that they did not have AF were eligible for the control group. Controls were identified as follows. For each confirmed AF case, 10 women without AF at the time of the index date were randomly selected from the pool of women in the birth cohort who met the following criteria using a greedy matching algorithm: (1) woman's year of birth ($\pm$3 years); (2) age at first pregnancy lasting >20 weeks ($\pm$4 years); (3) lifetime parity ($\pm$1 if parity <4, otherwise a match if $\geq$4); and (4) contact with a REP-affiliated provider within $\pm$3 years of the case's index date. The medical records of the controls were reviewed to confirm criteria (2) and (3), and the first woman among the set of 10 who met all of the above criteria and had sufficient pregnancy information in her records to apply the algorithm for the definition of HPD was selected.

Chart Abstraction

Data relevant to the AF diagnosis and pregnancy information, including all blood pressure, urinary protein and laboratory values, for cases and controls were systematically abstracted from individual medical charts and recorded in an electronic database (REDcap, Nashville, TN). As multiple abstractors were involved in the process, interobserver variability was

tested on multiple occasions throughout the abstraction process. Where variations in abstracted data were observed, the charts were reviewed, and differences were resolved by consensus. For each systematic difference observed (≥2 charts with the same variation), presumed to be because of variations in interpretation of the abstraction manual, discrepancies were resolved by discussion within the entire research group and all previously abstracted records were re-reviewed to correct the discrepancy.

Definitions

AF was defined as a physician diagnosis of AF or atrial flutter recorded in the patient medical chart. Data relevant to the AF diagnosis, including the initial diagnosis, symptoms at presentation, and outcome (whether paroxysmal, persistent, or permanent), were recorded. Women who were diagnosed with AF before their first pregnancies were excluded.

Using the abstracted data, we developed electronic diagnostic algorithms for the diagnoses of HPD, as previous work has revealed poor sensitivity and specificity of HPD diagnostic codes compared with physician diagnoses in this[17] as well as other cohorts.[18,19] The exposure of interest was any form of HPD, including gestational hypertension, chronic hypertension, preeclampsia, preeclampsia superimposed on chronic hypertension, and/or eclampsia in any pregnancy. The definitions of all HPDs were developed by the research group to mimic how providers currently make these diagnoses (Table S2).[17] Because this study also focused on the interim development of hypertension after hypertensive pregnancy, any woman diagnosed with chronic hypertension before her first pregnancy was excluded. Women diagnosed with chronic hypertension at the time of pregnancy were included.

The diagnosis of chronic hypertension outside of pregnancy required 2 consecutive outpatient systolic blood pressures >140 mm Hg or diastolic blood pressures >90 mm Hg, or the use of antihypertensive medication. Diabetes mellitus was defined as physician-documented diabetes mellitus, a fasting blood glucose ≥126 mg/dL on 2 separate occasions, or a positive oral glucose tolerance test. Dyslipidemia was defined as provider-documented diagnosis, use of lipid-lowering agent or total cholesterol ≥200 mg/dL, high-density lipoprotein <40 mg/dL, or triglyceride level ≥150 mg/dL on a sample drawn after an overnight fast. Smoking was defined as ever having smoked. Heavy alcohol use was defined as >7 drinks/wk or provider documentation of heavy alcohol use. Thyroid disease was defined as a composite diagnosis of hypo- or hyperthyroidism. Composite lung disease was defined as a composite of asthma, chronic obstructive pulmonary or parenchymal lung disease. Chronic kidney disease included diagnoses of chronic kidney disease, end-stage renal disease, or proteinuria.

Coronary artery disease included both subclinical (eg, positive computed tomography coronary calcium score) and clinical coronary heart disease. The diagnosis of cerebrovascular disease was based upon history of a cerebrovascular event or imaging evidence of cerebrovascular disease (eg, cerebral infarct on imaging) or carotid disease. Rheumatic or other valvular disease was defined as a history of primary valve disease associated with at least moderate valve dysfunction. "Other structural heart disease" was defined as any structural heart disease that could not be potentially attributed to hypertension or other conditions listed in Table S3.

Statistical Analysis

Patient characteristics were compared between the AF cases and controls using the 2-sample t test or Wilcoxon rank sum test for continuous or ordinal variables, and the χ^2 test or Fisher exact test for categorical variables, as appropriate. Conditional logistic regression models were fit to evaluate the association between exposure status (HPD) and case–control status, both with and without adjustments for current hypertension, prepregnancy obesity, or both. The odds ratio and corresponding 95% confidence interval for preeclamptic pregnancy were estimated from the parameter estimates in each model as an estimate of the relative risk. All calculated P values were 2-sided and P values <0.05 were considered statistically significant. Statistical analyses were performed using the SAS version 9.2 software package (SAS Institute, Inc; Cary, NC).

Results

Selection of Cases

We identified 147 of the 7566 women who had diagnostic codes for AF and provided research authorization for the site where the AF was coded (Figure). Review of medical records revealed that 36 women did not have AF, yielding a positive predictive value of 75.8% for the diagnostic codes. The false-positive AF codes included situations where the diagnosis of AF was queried and subsequently disproved; a different arrhythmia, most commonly, supraventricular tachycardia, was diagnosed (and, we believe, was miscoded); the patient reported "heart fluttering" and atrial flutter was coded; no record of AF, palpitations, or anything similar was found in the chart and we believed that the presence of a code for AF was likely a coding error. Seven additional women were excluded because of inability to access or locate pregnancy information, and 1 was excluded because of a diagnosis of hypertension before her first pregnancy. After reviewing 761 potential controls for appropriate matching characteristics, 2

were found to have been diagnosed with AF, but had no diagnostic code for AF in the REP database. These women were retained as matched controls as the date of their AF diagnoses occurred after the AF diagnoses of their matched cases. They were also added to our case list. Therefore, 105 women met our inclusion criteria for cases (Figure). A single episode of AF was noted in 28.6% of cases (n=30), 54.3% (n=57) had paroxysmal AF, 2.9% (n=3) had persistent AF, and 14.3% (n=15) had permanent AF.

Patient Characteristics

Table 1 shows the characteristics of the 105 cases and their corresponding matched controls. The mean age of the cases was 57±8 years (mean±SD) at the time of the diagnosis of AF (56±8 years for controls), which occurred, on average, 32±8 years after the first pregnancy, (31±8 years for controls). Almost all of the women were white and had at least a high school–level education. Women with AF were more likely to have chronic medical conditions such as diabetes mellitus, hypertension, dyslipidemia, and thyroid, lung, and kidney

Figure. Flow chart demonstrating case selection. *Patients with insufficient pregnancy information had no or minimal prenatal records available for at least 1 pregnancy. The algorithm for the definition of hypertensive pregnancy disorders could therefore not be applied. AF indicates atrial fibrillation.

disease. They were also more likely to have been obese during their reproductive years (Table 2). Coronary artery disease, congestive heart failure, and rheumatic or other valvular disease were identified almost exclusively in cases.

The cases and controls were well matched on their pregnancy characteristics (Table 2). The mean age of first delivery was 24 years in the cases and 25 years in the controls with a majority of women having a parity of 3 or more in both cases and controls. The total number of pregnancies (lasting >20 weeks gestation) was 338 in the cases and 313 in controls.

HPD and AF

Table 3 shows the prevalence of HPDs in cases and controls. The number of cases with at least 1 HPD was 28 (26.7%) and of controls was 12 (11.4%). When all pregnancies were considered, the proportion of hypertensive pregnancies in the case group was 42/338 (12.4%) and in the control group was 14/313 (4.4%). No woman in either group had preeclampsia superimposed on chronic hypertension. The odds of having a HPD were higher in women with AF: 26.7% of cases versus 11.4% of controls, (odds ratio [95% confidence interval]: 2.60 [1.21–6.04]; model 1 in Table 4). This relationship was attenuated after adjustments for current hypertension (model 2), obesity during pregnancy (model 3), or both (model 4). When the exposure of preeclampsia was considered, there was no significant difference between cases and controls: 10.5% of cases versus 5.7% of controls; odds ratio (95% confidence interval): 1.83 (0.62–6.04). The difference in all HPDs between cases and controls was similar after excluding 19 case–control pairs with rheumatic or other valvular disease and other structural heart disease (Table 5).

Discussion

The presented results indicate that women with AF are 2.6 times more likely to have a history of a HPD compared with women without AF, a finding at least partially mediated by associated obesity and the development of hypertension following pregnancy. Our study also demonstrates the importance of previously published risk factors for AF in this population, including hypertension, coronary and structural heart disease, and obesity.

HPDs and cardiovascular disease, including AF, are intimately associated, with metabolic syndrome providing a key link between them (Figure S1). Of the directly modifiable risk factors for AF, components of the metabolic syndrome—hypertension and obesity—are the most significant.[2] The increasing prevalence of overweight and obesity worldwide,[20] aside from increasing AF prevalence, may also partially account for the increase in HPD prevalence.[8,21] The increase
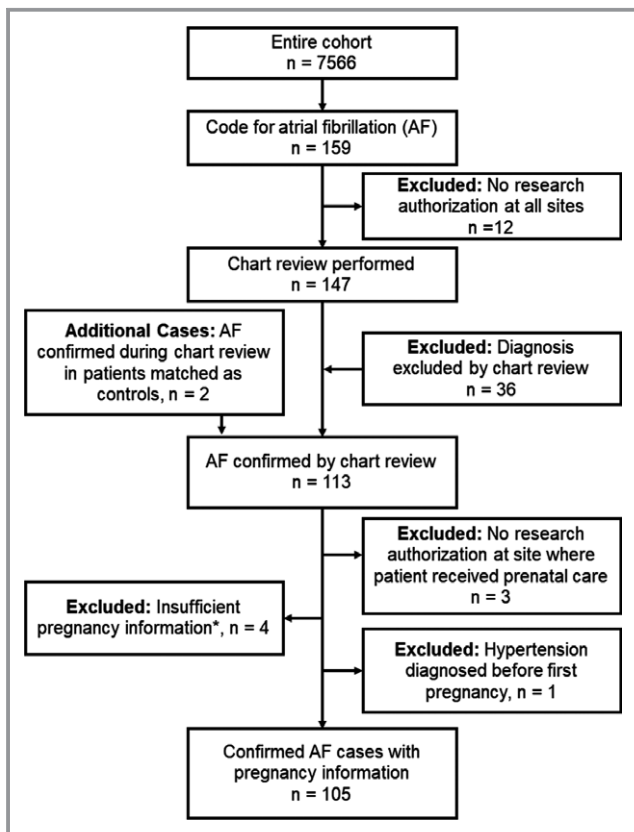
Table 1. Characteristics at the Time of the Index Date

Characteristic	AF Cases (N=105)	Controls (N=105)	P Value*
Patient Demographics			
Age at index date (y), mean (SD)	56.56 (8.01)	56.36 (7.71)	0.86
Years between first pregnancy and index date, mean (SD)	32.11 (8.11)	31.40 (7.59)	0.51
Race, n (%)			0.50
White	103 (98.1%)	105 (100.0%)	
Nonwhite	2 (1.9%)	0 (0.0%)	
Highest level of education, n (%)			0.13
Less than high school graduate	4 (3.8%)	3 (2.9%)	
High school graduate or GED/adult diploma	35 (33.3%)	25 (23.89%)	
Some college	36 (34.3%)	40 (38.1%)	
College graduate or more	27 (25.7%)	34 (32.4%)	
Unknown	3 (2.9%)	3 (2.9%)	
Comorbidities			
Hypertension, n (%)	62 (59.0%)	42 (40.0%)	0.006
Diabetes mellitus, n (%)	13 (12.4%)	3 (2.9%)	0.009
Dyslipidemia, n (%)	70 (66.7%)	54 (51.4%)	0.03
Ever smoked, n (%)	54 (51.4%)	47 (44.8%)	0.33
Alcohol, n (%)			0.057
No use	26 (24.8%)	28 (26.7%)	
Light or moderate use	71 (67.6%)	76 (72.4%)	
Heavy use	8 (7.6%)	1 (1.0%)	
Thyroid disease, n (%)	24 (22.9%)	10 (9.5%)	0.009
Obstructive sleep apnea, n (%)	10 (9.5%)	7 (6.7%)	0.45
Composite lung disease, n (%)	12 (11.4%)	1 (1.0%)	0.002
Chronic kidney disease, n (%)	14 (13.3%)	3 (2.9%)	0.005
Family history of AF, n (%)	14 (13.3%)	4 (3.8%)	0.014
Cardiovascular conditions			
Coronary artery disease, n (%)	19 (18.1%)	2 (1.9%)	<0.001
Peripheral vascular disease, n (%)	2 (1.9%)	0 (0.0%)	0.50
Cerebrovascular disease, n (%)	8 (7.6%)	3 (2.9%)	0.21
Congestive heart failure, n (%)	22 (21.0%)	0 (0.0%)	<0.0001
Hypertrophic cardiomyopathy, n (%)	0 (0.0%)	0 (0.0%)	. . .
Rheumatic or other valvular disease, n (%)	11 (10.5%)	1 (1.0%)	0.003
Other structural heart disease, n (%)	8 (7.6%)	2 (1.9%)	0.052

Index date for cases and controls is defined as the time of atrial fibrillation diagnosis in cases. AF indicates atrial fibrillation; GED, General Equivalency Diploma.
*P values derived from equal-variance *t* tests and Wilcoxon rank sum tests for continuous measures and χ^2 and Fisher exact test for categorical measures.

in AF in women with a history of HPD may be as a direct consequence of persistent structural and functional myocardial changes that occur during HPDs; or future hypertension that occurs earlier in life[6] and at higher rates in women with HPD versus those with normotensive pregnancies.[5] An echocardiographic study evaluating the prevalence of left ventricular hypertrophy following hypertensive pregnancy showed that the increase in prevalence was likely explained by a longer duration of chronic hypertension.[13] The findings in our study are in keeping with this: women with HPDs develop hypertension and its consequences, including AF,[2] at higher rates than those without.

Table 2. Pregnancy Characteristics Among AF Cases and Non-AF Controls

Characteristic	AF Cases (N=105)	Controls (N=105)	P Value*
Age at first delivery (y), mean (SD)	24.44 (4.53)	25.02 (4.64)	0.36
Total gravida per patient, n (%)			0.83
1	7 (6.7%)	6 (5.7%)	
2	27 (25.7%)	30 (28.6%)	
3+	71 (67.6%)	69 (65.7%)	
Total parity per patient, n (%)[†]			0.74
1	11 (10.5%)	6 (5.7%)	
2	31 (29.5%)	41 (39.0%)	
3+	63 (60.0%)	58 (55.2%)	
Total number of live births	335	311	...
Total number of stillbirths	3	2	...
Total number of pregnancies <20 wks	59	42	...
BMI>30 at any first prenatal visit[†], n (%)[‡]	18 (17.1%)	3 (2.9%)	<0.001

AF indicates atrial fibrillation; BMI, body mass index.
*P values derived from equal variance t tests and Wilcoxon rank sum tests for continuous and ordinal measures and χ^2 and Fisher exact test for categorical measures
[†]Parity: any live or stillbirth >20 wks.
[‡]First prenatal visit was restricted to occur before 20 gestational wks.

The current study is the first to directly evaluate the relationship between the HPDs and AF, specifically. This study expands on prior work done by Ray et al, who noted an increased risk of heart failure and dysrhythmias after maternal placental syndromes, which include the HPDs.[22] They, however, considered all arrhythmias, atrial and ventricular, as a group, rather than individually.

AF causes significant morbidity and mortality in women. Although absolute incidence rates for AF are lower in women compared with men, the risk of stroke and other thromboembolic events associated with AF is higher in women than in men worldwide.[3,23] In the Copenhagen City Heart Study, the cardiovascular mortality for AF in women was found to be 2.5 times higher than in men.[24] AF in women, therefore, deserves heightened attention.

A recent report from the Framingham study showed an increasing prevalence of AF despite improved hypertension treatment with declining blood pressure levels and a reduction

Table 3. HPDs, Per-Subject and Per-Pregnancy

| Hypertensive Pregnancy Disorder | Per Subject* | | Per Pregnancy >20 Wks | |
	AF Cases (N=105)	Controls (N=105)	AF Cases (N=338)	Controls (N=313)
Normotensive pregnancy	77	93	284	289
Chronic HTN	2	1	5	1
Gestational HTN	15	5	24	7
PE				
PE-definite	8	2	9	2
PE-probable	2	3	3	3
PE-possible	0	1	0	1
PE-superimposed[†]	0	0	0	0
Eclampsia	1	0	1	0
Insufficient information	0	0	12	10

AF indicates atrial fibrillation; HPD, hypertensive pregnancy disorders; HTN, hypertension; PE, preeclampsia.
*Based on worst HPD diagnosis.
[†]Superimposed on chronic HTN.

Table 4. Association Between Exposure (Any HPD or Preeclampsia Specifically) With Future AF (Per Woman), With and Without Adjusting for Hypertension* and BMI >30[†]

Factor	Model 1 Unadjusted		Model 2 Adjusted for Hypertension		Model 3 Adjusted for BMI		Model 4 Adjusted for Both	
	OR (95% CI)	P Value[‡]	Adjusted OR (95% CI)	P Value[‡]	Adjusted OR (95% CI)	P Value[‡]	Adjusted OR (95% CI)	P Value[‡]
Any HPD[§]	2.60 (1.21–6.04)	0.011	2.07 (0.92–4.96)	0.068	2.40 (1.08–5.78)	0.021	2.12 (0.92–5.23)	0.061
Hypertension*	…	…	1.82 (0.96–3.53)	0.054	…	…	1.41 (0.72–2.83)	0.34
BMI >30[†]	…	…	…	…	5.48 (1.56–9.50)	0.003	4.60 (1.25–25.59)	0.013
Preeclampsia[¶]	1.83 (0.62–6.04)	0.33	1.33 (0.42–4.57)	0.62	1.46 (0.47–4.98)	0.61	1.20 (0.37–4.21)	0.80
Hypertension*	…	…	2.08 (1.12–4.00)	0.016	…	…	1.64 (0.85–3.25)	0.13
BMI >30[†]	…	…	…	…	5.67 (1.64–30.18)	0.002	4.42 (1.22–24.29)	0.014

AF indicates atrial fibrillation; BMI, body mass index; CI, confidence interval; HPD, hypertensive pregnancy disorder; OR, odds ratio.
*Hypertension at the time of index date.
[†]BMI >30 at any first prenatal visit.
[‡]Exact *P* value derived from score statistic from fitting a conditional logistic regression model.
[§]The prevalence of HPD was 26.7% (28/105) and 11.4% (12/105) among AF cases and controls, respectively.
[¶]The prevalence of preeclampsia was 10.5% (11/105) and 5.7% (6/105) among AF cases and controls, respectively.

in the prevalence of electrocardiographic left ventricular hypertrophy.[2] The increase in prevalence was associated with a decline in mortality, suggesting that increased surveillance and subsequent appropriate treatment may have been partly responsible for the increasing prevalence. The knowledge of the increased risk for AF in women with HPD presents a unique opportunity for targeted surveillance and points towards a possible role of sex-specific factors, including pregnancy-related complications. A worrisome trend has recently been demonstrated: women with severe forms of preeclampsia are at risk for cardiovascular death as early as the first decade after their affected pregnancies.[25] Given the significant impact of AF on morbidity and mortality in women, our study, further supported by previous epidemiological studies, emphasizes the need to (1) include a history of HPD

in a typical cardiovascular history and in risk stratification schemes; and (2) survey affected women for modifiable risk factors and early cardiovascular disease, including AF, for timely preventive and treatment strategies, respectively.

Limitations

This is a retrospective study. Blood pressure was measured during routine clinical care and methods of blood pressure measurement were not standardized. Our use of diagnostic codes may have resulted in the exclusion of women within the cohort who had been diagnosed with AF but had no code within the REP, though our review of >700 potential controls for matching only identified 2 cases of AF, suggesting that any effect was minor. We also cannot account for women with

Table 5. Sensitivity Analysis: Association Between Exposure (Any HPD or Preeclampsia Specifically) With Future AF (Per Woman), With and Without Adjusting for Hypertension* and BMI >30[†], After Exclusions[‡] (n=86 Cases and Controls)

Factor	Model 1 Unadjusted		Model 2 Adjusted for Hypertension		Model 3 Adjusted for BMI		Model 4 Adjusted for Both	
	OR (95% CI)	P Value[§]	Adjusted OR (95% CI)	P Value[§]	Adjusted OR (95% CI)	P Value[§]	Adjusted OR (95% CI)	P Value[§]
Any HPD[∥]	2.63 (1.12, 6.85)	0.024	2.09 (0.85–5.62)	0.11	2.32 (0.96–6.19)	0.050	2.04 (0.82–5.54)	0.10
Hypertension*	…		1.95 (0.96–4.17)	0.050	…		1.53 (0.71–3.39)	0.28
BMI >30[†]	…		…		4.37 (1.21–23.84)	0.013	3.47 (0.89–19.85)	0.058
Preeclampsia[#]	1.40 (0.38, 5.59)	0.77	1.08 (0.28–4.53)	1.00	1.13 (0.29–4.68)	1.00	0.98 (0.25–4.13)	1.00
Hypertension*	…		2.27 (1.14–4.77)	0.013	…		1.77 (0.84–3.86)	0.12
BMI >30[†]	…		…		4.88 (1.38–26.39)	0.007	3.54 (0.92–20.12)	0.060

AF indicates atrial fibrillation; BMI, body mass index; CI, confidence interval; HPD, hypertensive pregnancy disorder; OR, odds ratio.
*Hypertension at the time of index date.
[†]BMI >30 at any first prenatal visit.
[‡]After excluding 19 women who had other structural heart disease or rheumatic or other valvular disease and their matched pairs.
[§]Exact *P* value derived from score statistic from fitting a conditional logistic regression model.
[∥]The prevalence of HPD was 26.7% (23/86) and 11.6% (10/86) among AF cases and controls, respectively.
[#]The prevalence of preeclampsia was 8.1% (7/86) and 5.8% (5/86) among AF cases and controls, respectively.

undiagnosed AF, with or without HPDs. This is a relatively small study with limited power to evaluate for independent associations. Larger studies should be performed to confirm and extend these findings. Olmsted County has a predominantly white population, and this is reflected in the demographics of our sample. We therefore may not be able to generalize this study to a population of more varied ethnicity.

Strengths

We reviewed each case with a diagnostic code for accuracy, which improves the rigor of the study. The 75% positive predictive value of diagnostic codes found in our sample is of concern, and may have significant implications for some larger studies involving administrative databases.

Conclusions

Women with HPDs are at risk for development of AF later in life. The development of a HPD should be treated as an opportunity to improve the management of modifiable cardiovascular risk factors, particularly hypertension and obesity. Further studies should be done in larger cohorts to determine the generalizability of our findings, as well as to evaluate the cost effectiveness of screening women with a history of HPD for AF to reduce their morbidity and mortality from this condition.

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Disclosures

None.

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Supplemental Material

Table S1. Diagnostic codes used to screen for cases of atrial fibrillation and flutter.

ICD-9 codes	
427.3	ATRIAL FIBRILLATION AND FLUTTER
427.31	ATRIAL FIBRILLATION
427.32	ATRIAL FLUTTER

Mayo adapted HICDA codes	
4163000	FIBRILLATION, ATRIAL
4163110	FIBRILLATION, WITH FLUTTER
4163111	SYNDROME, FIBRILLATION-FLUTTER
4163210	FIBRILLATION, ATRIAL, NOS - AF
4163211	FIBRILLATION, AURICULAR, SEE ALSO FIBRILLATION, ATRIAL
4163220	FIBRILLATION, ATRIAL, CHRONIC
4163230	FIBRILLATION, ATRIAL, PAROXYSMAL--PAF
4163240	FIBRILLATION, ATRIAL, ACUTE
4164000	FLUTTER, ATRIAL
4164110	FLUTTER, AURICULAR

4164111   FLUTTER, ATRIAL

4169150   FIBRILLATION, NOS (HEART#)

Table S2. Diagnostic algorithms for Hypertensive Pregnancy Disorders.

HPD	Timing	Blood pressure criteria	Additional criteria for diagnosis
Gestational Hypertension	1. After 20 weeks' gestation and up to 24 hours post-delivery 2. First hypertensive reading must be before admission for delivery	Any of the following: 1. If only 2 readings available, then both have SBP> 140 OR DBP>90, occurring ≥ 6 hours apart but within 1 month. 2. If 2 or more BPs available after the initial hypertensive reading, then at least 50% of the BP measurements must have SBP > 140 OR DBP > 90. 3. One SBP>140 OR DBP>90 AND started on an anti-hypertensive medication the same day, prior to admission	
Preeclampsia-definitive	1. Same as above for gestational hypertension	Same as above	One of the following on at least 1 occasion:

2. All new lab abnormalities must be between 1 week prior to and up to 72 hours post-delivery, unless specified otherwise	1. New onset proteinuria: dipstick 1+ OR proteinuria >0.300 g/24 hours OR protein/osmolality ratio of >0.3 2. Worsening chronic proteinuria: doubling of 24-hour urine protein or dipstick (1 to 2+ or 2 to 3) from value obtained < 20 weeks or pre-pregnancy 3. Magnesium sulfate given at or after admission for delivery up to 72 hours post delivery 4. Serum ALT or AST >70 U/L 5. Platelet count <100k 6. Serum creatinine >1.1 mg/dL, or doubling of serum Cr from a lab at <20 weeks' gestation

Preeclampsia – probable†	1. At or after admission for delivery and up to 24 hours post-delivery for blood pressure criteria 2. All new lab abnormalities must be between 1 week prior to and up to 72 hours post-delivery, unless specified otherwise	One SBP>140 OR DBP>90 OR taking an anti-hypertensive medication at or after admission for delivery and up to 24 hours post-delivery	Any of the criteria (1-6) for definitive preeclampsia on at least one occasion.
Chronic Hypertension‡	Prior to 20 weeks' gestation	Any of the following: 1. Minimum of 2 readings with SBP>140 OR DBP>90 mm Hg, which occurred ≥6 hours apart, but within 1 month 2. Taking an anti-hypertensive medication prior to 20 gestational weeks	

	3. A physician diagnosis of chronic hypertension prior to any pregnancy before 20 weeks' gestation		
Preeclampsia Superimposed on chronic hypertension	1. Same as above for chronic hypertension 2. Worsening of BP between 1 week prior to and up to 24 hours post-delivery 3. All new lab abnormalities must be between 1 week prior to and up to 72 hours post-delivery, unless specified otherwise	Worsening BP defined as: 1. An increase of SBP≥160 or DBP≥110 OR 2. Adding another BP medication	Any of the criteria (1-6) for definitive preeclampsia on at least one occasion.
Eclampsia (definite/probable)	Must meet criteria for either gestational hypertension, preeclampsia, or preeclampsia superimposed on chronic hypertension.		Definite – Seizures or change in mental status observed in the hospital

	Probable – Seizures witnessed as an outpatient.

*Blood pressures were only taken from hospital or outpatient visits, not ER visits to exclude blood pressure elevation due to other causes, such as acute illness or pain. †The diagnosis of probable preeclampsia reflects the difficulty in a retrospective diagnosis of preeclampsia, where some clinical information may not be available to make a definitive diagnosis, but the clinical presentation is highly suggestive of preeclampsia. For the purposes of analysis, probable preeclampsia was considered a preeclamptic pregnancy. ‡A diagnosis of chronic hypertension precluded a diagnosis of gestational hypertension in the same pregnancy.

Table S3. Conditions included in structural heart disease and primary valve disease headings.

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Structural heart disease	Cardiomyopathy due to myotonic dystrophy
	Cardiomyopathy due to chemotherapy
	Lyme carditis
	Radiation related restrictive cardiomyopathy
Primary valve disease	Rheumatic valve disease (native or prosthetic valve)
	Cleft mitral valve
	Radiation induced valve disease
	Mitral valve endocarditis
	Mitral valve prolapse (native or prosthetic valve)
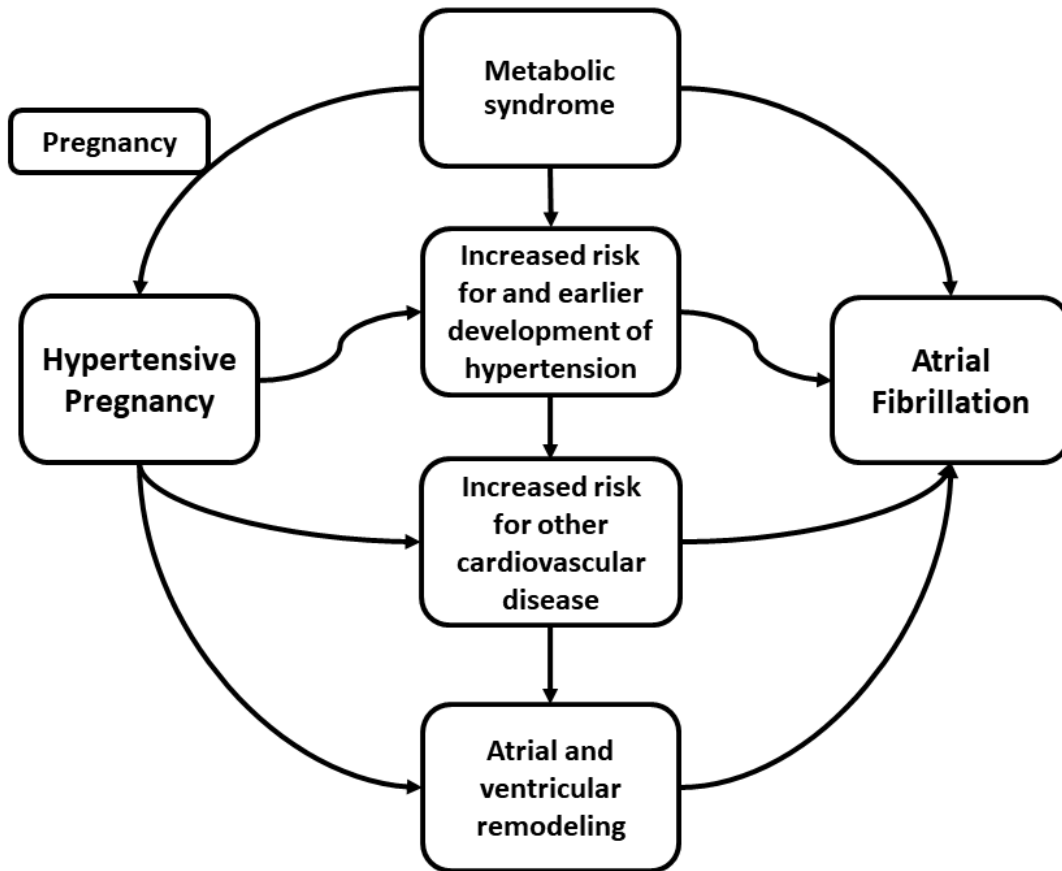
Figure S1. The relationship between hypertensive pregnancy disorders (HPDs) and atrial fibrillation (AF). Multiple potential mechanisms for a link between the two disorders exist.