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ORIGINAL RESEARCH

Trends, Predictors, and Outcomes of Cardiovascular Complications Associated With Polycystic Ovary Syndrome During Delivery Hospitalizations: A National Inpatient Sample Analysis (2002–2019)

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BACKGROUND: Women with polycystic ovary syndrome (PCOS) have an increased risk of pregnancy-associated complications. However, data on peripartum cardiovascular complications remain limited. Hence, we investigated trends, outcomes, and predictors of cardiovascular complications associated with PCOS diagnosis during delivery hospitalizations in the United States.

METHODS AND RESULTS: We used data from the National Inpatient Sample (2002–2019). *International Classification of Diseases, Ninth Revision* (*ICD-9*), or *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes were used to identify delivery hospitalizations and PCOS diagnosis. A total of 71 436 308 weighted hospitalizations for deliveries were identified, of which 0.3% were among women with PCOS (n=195 675). The prevalence of PCOS, and obesity among those with PCOS, increased during the study period. Women with PCOS were older (median, 31 versus 28 years; $P<0.01$) and had a higher prevalence of diabetes, obesity, and dyslipidemia. After adjustment for age, race and ethnicity, comorbidities, insurance, and income, PCOS remained an independent predictor of cardiovascular complications, including preeclampsia (adjusted odds ratio [OR], 1.56 [95% CI, 1.54–1.59]; $P<0.01$), eclampsia (adjusted OR, 1.58 [95% CI, 1.54–1.59]; $P<0.01$), peripartum cardiomyopathy (adjusted OR, 1.79 [95% CI, 1.49–2.13]; $P<0.01$), and heart failure (adjusted OR, 1.76 [95% CI, 1.27–2.45]; $P<0.01$), compared with no PCOS. Moreover, delivery hospitalizations among women with PCOS were associated with increased length (3 versus 2 days; $P<0.01$) and cost of hospitalization ($4901 versus $3616; $P<0.01$).

CONCLUSIONS: Women with PCOS had a higher risk of preeclampsia/eclampsia, peripartum cardiomyopathy, and heart failure during delivery hospitalizations. Moreover, delivery hospitalizations among women with PCOS diagnosis were associated with increased length and cost of hospitalization. This signifies the importance of prepregnancy consultation and optimization for cardiometabolic health to improve maternal and neonatal outcomes.

Key Words: cardiovascular disease ■ eclampsia ■ polycystic ovary syndrome ■ preeclampsia

Polycystic ovary syndrome (PCOS) is an endocrine disorder characterized by irregular menstrual cycles (ovulatory dysfunction), hyperandrogenism, and polycystic-appearing ovaries on imaging, mostly seen in women of reproductive age.[1–4] PCOS affects women across all races

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CLINICAL PERSPECTIVE

What Is New?

- Polycystic ovary syndrome is independently associated with an increased risk of acute cardiovascular complications at the time of delivery hospitalization, including peripartum cardiomyopathy, acute heart failure, pulmonary edema, and venous thromboembolism.
- This association of polycystic ovary syndrome with these acute cardiovascular complications at delivery remains significant even after further adjustment for preeclampsia/eclampsia risk.

What Are the Clinical Implications?

- Our study stresses the importance of optimizing the cardiovascular health of women with polycystic ovary syndrome before, during, and after pregnancy to prevent adverse cardiovascular complications.

Nonstandard Abbreviations and Acronyms

NIS	National Inpatient Sample
PCOS	polycystic ovary syndrome

and ethnicities, and its prevalence is reported to be 3% to 10%.[5,6] The association between PCOS and the development of cardiovascular risk factors is well established.[1] PCOS is associated with incident hypertension,[7,8] and women with PCOS have a 2-fold higher risk of developing type 2 diabetes.[9] Half of patients with PCOS are obese and have an increased prevalence of sleep apnea and dyslipidemia.[5,6,9,10] Moreover, women of reproductive age with PCOS are at increased risk for incident cardiovascular disease (CVD) events later in life.[4,11–13]

Women with PCOS may also have an increased risk of pregnancy-associated complications,[14] such as gestational diabetes, preeclampsia, and preterm delivery,[15] as well as complications in the postpartum period.[16] There has been increasing awareness of the long-term cardiovascular risks associated with a history of adverse pregnancy outcomes.[17,18] Hypertensive disorders of pregnancy, notably preeclampsia, are also associated with acute cardiovascular complications at the time of delivery, including peripartum cardiomyopathy and heart failure.[19,20] However, limited data exist on whether PCOS independently confers increased risk of cardiovascular complications during the peripartum period. Contemporary trends in the prevalence of PCOS among child-bearing women in the United States and resource use in terms of length and cost of hospital stay also remain to be explored.

Therefore, we aimed to study the trends, outcomes, and predictors of cardiovascular complications associated with PCOS during delivery hospitalizations using a US nationwide real-world population database.

METHODS

The National Inpatient Sample (NIS) data are publicly available. The specific data supporting this study's findings are available from the corresponding author on request.

Study Data

This study used data from the NIS database from 2002 to 2019. The NIS is one of several databases managed by the Agency for Healthcare Research and Quality through a federal-state-industry partnership called the Healthcare Cost and Utilization Project.[21] The NIS contains administrative claims data from >7 million inpatient hospitalizations annually in 47 participating states plus the District of Columbia, representing >97% of the US population. Because NIS data are compiled annually, the data can be used for the analysis of disease trends over time using trend weights compiled by the Healthcare Cost and Utilization Project.[21] For the cost of care, charge/cost ratio supplied by Healthcare Cost and Utilization Project derived from Centers for Medicare & Medicaid Services was applied to total hospital charges. Institutional Review Board approval and informed consent were not required for this study because NIS data are deidentified and publicly available. In compliance with Healthcare Cost and Utilization Project guidelines, observations with a cell count of <11 are reported as "<11."[22]

Study Design and Data Selection

We analyzed NIS data using *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*), and *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*), claims codes. We first identified delivery hospitalizations using *ICD-9-CM* and *ICD-10-CM* codes (Table S1). Among the selected cases, we used *ICD-9-CM* code 256.4 and *ICD-10-CM* code E28.2 to identify delivery hospitalizations with PCOS. All diagnosis fields were queried to select and categorize the study population. Individuals aged <18 years were excluded from the study. An illustration of the key study design and findings and detailed methods flowsheet are presented in Figures 1 and 2.

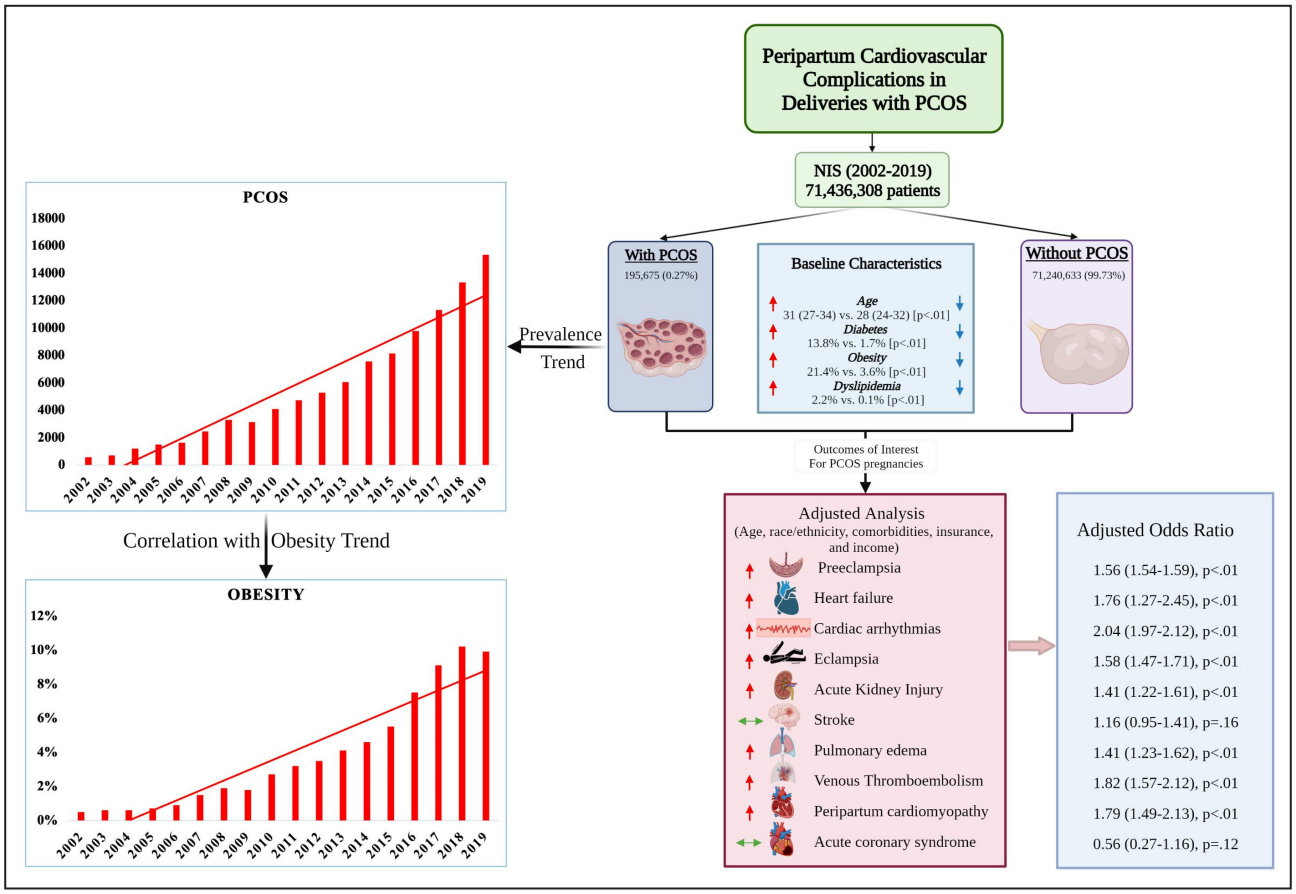

Figure 1. Trends, predictors, and outcomes of cardiovascular complications associated with polycystic ovary syndrome (PCOS) during delivery hospitalizations: a National Inpatient Sample (NIS) analysis.

Study End Point

The primary study end points were preeclampsia, peripartum cardiomyopathy, and heart failure. Secondary end points included eclampsia, acute coronary syndrome, ischemic and hemorrhagic stroke, pulmonary edema, cardiac arrhythmias, acute kidney injury, venous thromboembolism, length of stay, and cost of hospitalization. Associated procedures and complications were identified using *ICD-9-CM* and *ICD-10-CM* codes (Table S1).

Statistical Analysis

Descriptive statistics were presented as frequencies with percentages for categorical variables and as medians with interquartile range for continuous variables. Baseline characteristics were compared using a Pearson χ^2 test and Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables. The *P* value for the slope was used to assess temporal trends. Unadjusted odds ratios (ORs) were derived using Cochran-Mantel-Haenszel test. A multivariable logistic regression model was fitted to test the association of PCOS with in-hospital outcomes, adjusted for age, race and ethnicity, hospital region, chronic hypertension, diabetes, dyslipidemia, heart failure, chronic kidney disease, coronary artery disease, obesity, smoking, multiple gestation, cesarean delivery, median household income, and primary insurance. A second logistic regression model was developed, which, in addition to the aforementioned variables, adjusted for preeclampsia and eclampsia to test the independent association of PCOS with cardiovascular complications. We further assessed these same covariates as potential predictors of preeclampsia among women with PCOS.

All missing values in the data set are reported in the table of hospitalization characteristics (Table 1). The missing data were predominantly present in the race and ethnicity variable (15%). Missing data were minimal in the primary insurance payer variable (0.2%) and median household income variable (1.6%). Because of the inability to assess the pattern of missingness and the overall large sample size relative to the missing values, multiple imputation was not performed. For logistic regression, missing values were not included in

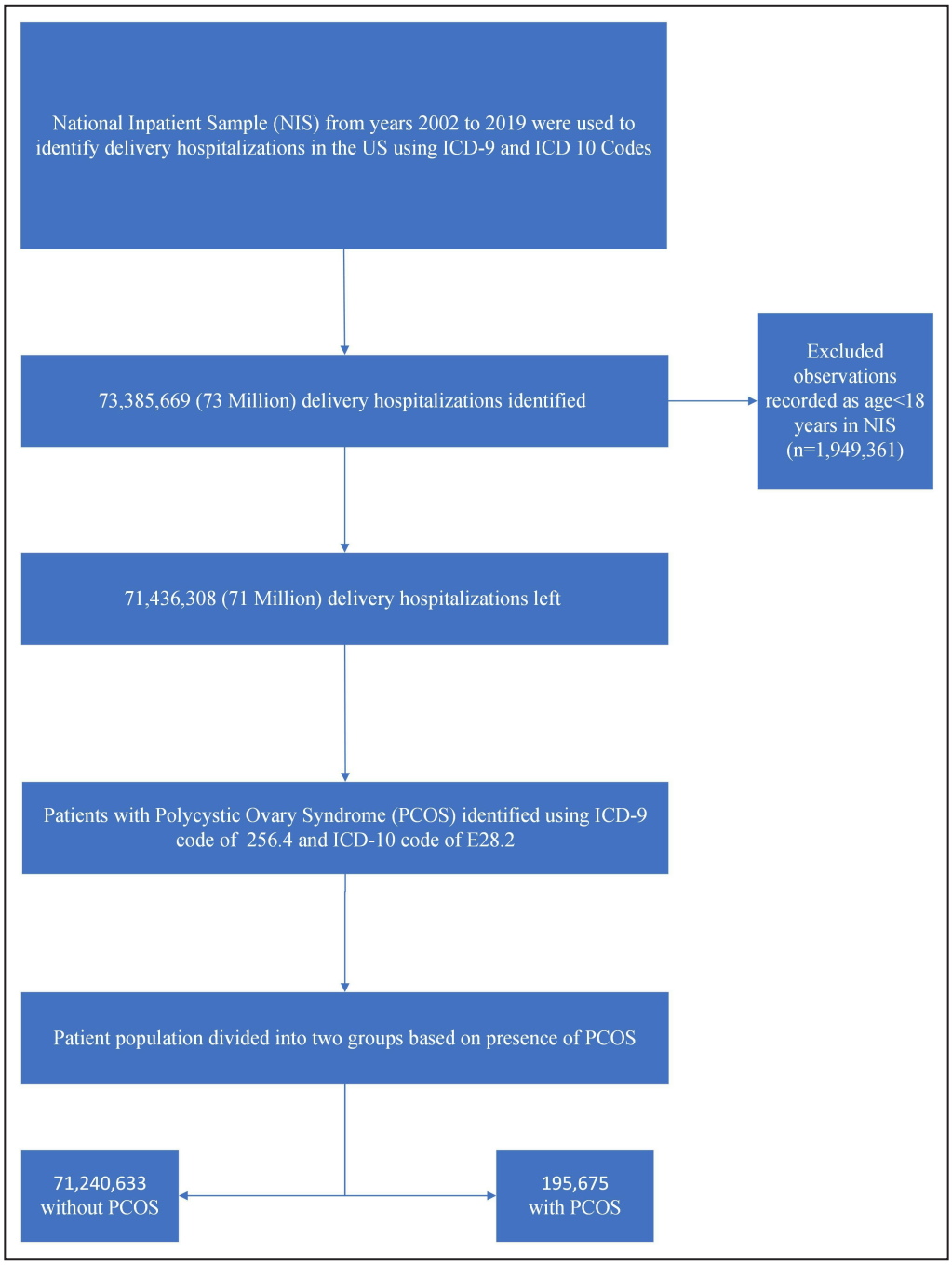

Figure 2. Study flowchart.
ICD-9 indicates *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision*; NIS, National Inpatient Sample; and PCOS, polycystic ovary syndrome.

the analysis. Further supplementary analysis was also performed to evaluate the effect of removing missing values from the primary analysis. For this purpose, we selected race and ethnicity variable and recoded missing values with "other." Logistic regression analysis to test the association between PCOS and primary/secondary outcomes was performed again after incorporating the missing values from the race and ethnicity variables. In Data S1, missing values in the primary insurance payer and median household income variables were not included, given that the overall number of missing values were <1.6% and hence assumed to be missing at random.

All statistical analyses were performed using Statistical Package for Social Science version 27 (IBM Corp). Given the complex survey design of NIS, sample weights, clusters, and strata were applied to generate US national estimates.

RESULTS

Hospitalization Characteristics of the Study Population

A total of 71 436 308 weighted hospitalizations for deliveries were identified in the United States from 2002 to 2019. Of the included patients, 0.3% had a diagnosis of PCOS (n=195 675). Patients with PCOS had a higher median (interquartile range) age of 31 (27–34) years compared with 28 (24–32) years for patients without PCOS (P<0.01). Women with PCOS were more likely to be White race (62.1% versus 44.7%) and less likely to be Black race (8.4% versus 12%) or Hispanic ethnicity (10.5% versus 18.8%) adults. In terms of comorbidities, diabetes (13.8% versus 1.7%), obesity (21.4% versus 3.6%), and dyslipidemia (2.2% versus 0.1%) were more frequent in the PCOS group when compared with patients without PCOS (P<0.01 for all). The detailed baseline characteristics are given in Table 1.

Trends for Prevalence of PCOS and Obesity

During the study duration, the prevalence of PCOS increased from 569 per 100 000 in 2002 to 15 349 per 100 000 deliveries in 2019 (Figure 3). Moreover, during this same period, there was an increase in the prevalence of obesity from 5.7% in 2002 to 28.2% in 2019 during delivery hospitalizations among women with PCOS (P<0.01 for all) (Figure 4).

Cardiovascular Complications Associated With PCOS and Hospital Resource Use

Patients with PCOS had a higher incidence of cardiovascular complications compared with patients without PCOS during delivery hospitalizations (Table 2). Patients with PCOS had higher rates of development of preeclampsia (10 255 versus 4353; P<0.01) per 100 000 deliveries. Similarly, PCOS was associated with higher rates of peripartum cardiomyopathy (81 versus 30; P<0.01) and heart failure (103 versus 44; P<0.01) per 100 000 deliveries. Other cardiovascular complications, including stroke, cardiac arrhythmias, pulmonary edema, and venous thromboembolism, were also more common with deliveries in women with PCOS. In terms of resource use, length of hospital stay was higher for deliveries among women with PCOS versus women without PCOS (3 versus 2 days; P<0.01). Similarly, deliveries for women with PCOS had a higher cost of hospitalization ($4901 versus $3616; P<0.01).

Table 1. Characteristics of Delivery Hospitalizations With and Without PCOS

Variable	Without PCOS (71 240 633)	With PCOS (195 675)	*P* value
Age, median (IQR), y	28 (24–32)	31 (27–34)	<0.01
Race or ethnicity			
White	31 854 198 (44.7)	121 459 (62.1)	<0.01
Black	8 536 587 (12.0)	16 359 (8.4)	
Hispanic	13 416 188 (18.8)	20 528 (10.5)	
Asian or Pacific Islander	3 310 366 (4.6)	12 001 (6.1)	
Native American	443 079 (0.6)	979 (0.5)	
Other*	2 911 374 (4.1)	6692 (3.4)	
Missing	10 768 841 (15.1)	17 657 (9.0)	
Hospital regions			
Northeast	11 785 641 (16.5)	34 674 (17.7)	<0.01
Midwest	15 216 290 (21.4)	50 579 (25.8)	
South	26 919 761 (37.8)	66 070 (33.8)	
West	17 318 941 (24.3)	44 352 (22.7)	
Chronic hypertension	478 910 (0.7)	3463 (1.8)	<0.01
Diabetes	1 200 732 (1.7)	26 918 (13.8)	<0.01
Dyslipidemia	92 826 (0.1)	4333 (2.2)	<0.01
Heart failure	44 633 (0.063)	247 (0.126)	<0.01
Chronic kidney disease	9637 (0.014)	60 (0.031)	<0.01
Coronary artery disease	8030 (0.011)	104 (0.053)	<0.01
Obesity	2 553 692 (3.6)	41 966 (21.4)	<0.01
Smoking	1 444 756 (2.0)	4029 (2.1)	0.33
Multiple gestation	1 341 454 (1.9)	11 053 (5.6)	<0.01
Cesarean delivery	22 112 011 (31.0)	90 056 (46.0)	<0.01
Preterm birth	5 318 491 (7.5)	19 846 (10.1)	<0.01
Still birth	481 511 (0.7)	2254 (1.2)	<0.01
Median household income			
0–25th Percentile	18 162 866 (25.5)	35 266 (18.0)	<0.01
26–50th Percentile	17 247 754 (24.2)	45 364 (23.2)	
51–75th Percentile	17 316 089 (24.3)	55 455 (28.3)	
76–100th Percentile	17 352 841 (24.4)	57 944 (29.6)	
Missing	1 161 083 (1.6)	1646 (0.8)	
Primary insurance			
Medicare	457 916 (0.6)	1636 (0.8)	<0.01
Medicaid	29 493 242 (41.4)	36 428 (18.6)	
Private insurance	36 985 864 (51.9)	149 067 (76.2)	
Self-pay	2 159 340 (3.0)	2141 (1.1)	
No charge	121 765 (0.2)	77 (0.0)	
Other*	1 914 272 (2.7)	6014 (3.1)	
Missing	108 234 (0.2)	312 (0.2)	

Results presented as number (percentage), unless otherwise indicated. IQR indicates interquartile range; and PCOS, polycystic ovary syndrome.
*Other depicts other race/ethnicities not listed or multiracial.

ORs for In-Hospital Complications

After adjustment for age, race and ethnicity, comorbidities, insurance, and income, PCOS remained an independent predictor of many cardiovascular complications (Figure 5 and Table S2). Patients with PCOS had higher risk for the development of preeclampsia

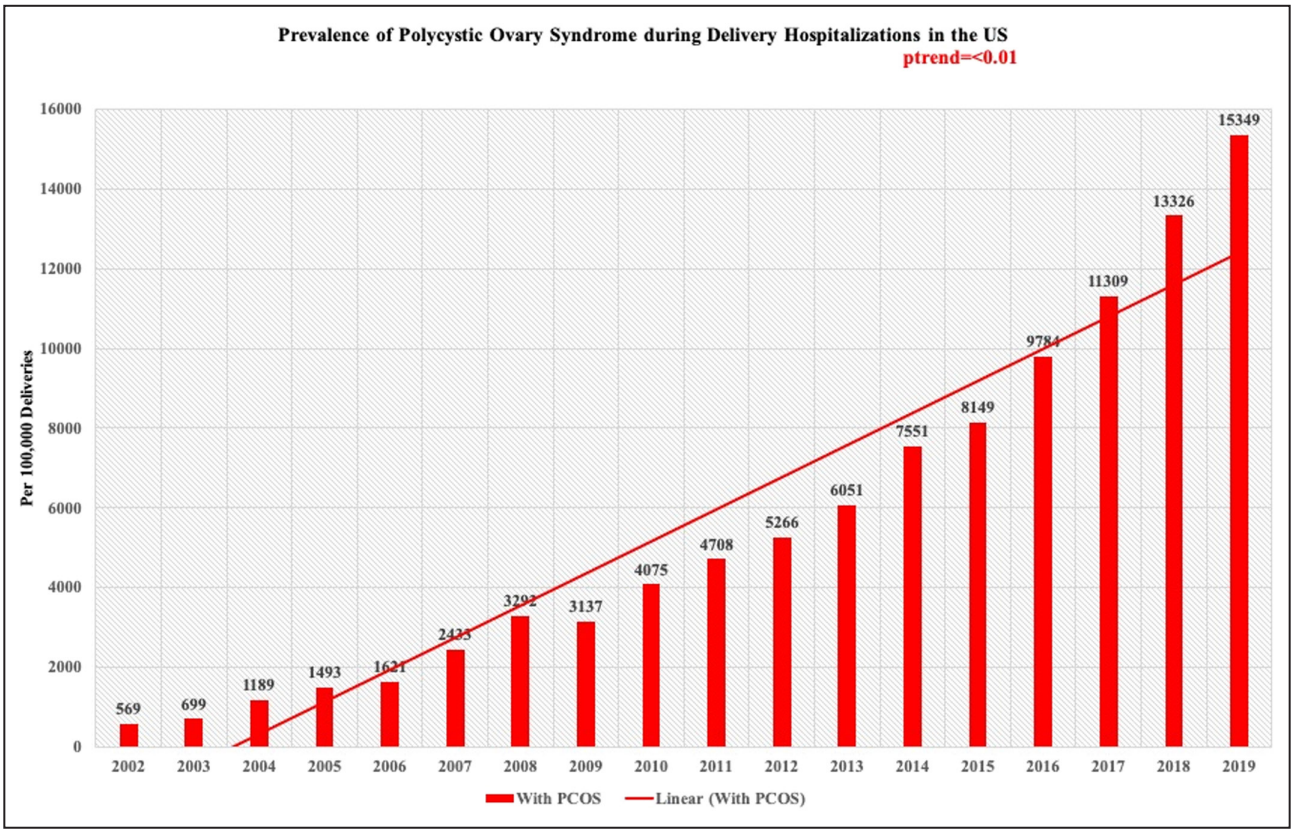

Figure 3. **Trends of prevalence of polycystic ovary syndrome (PCOS) during delivery hospitalizations.**

compared with patients without PCOS (adjusted OR [aOR], 1.56 [95% CI, 1.54–1.59]; *P*<0.01). Similarly, deliveries among women with a history of PCOS were associated with higher adjusted odds of eclampsia (aOR, 1.58 [95% CI, 1.47–1.71]; *P*<0.01), peripartum cardiomyopathy (aOR, 1.79 [95% CI, 1.49–2.13]; *P*<0.01), pulmonary edema (aOR, 1.41 [95% CI, 1.23–1.62]; *P*<0.01), acute kidney injury (aOR, 1.41 [95% CI, 1.22–1.61]; *P*<0.01), and venous thromboembolism (aOR, 1.82 [95% CI, 1.57–2.12]; *P*<0.01), compared with delivery hospitalizations for women without PCOS. However, the odds of acute coronary syndrome and stroke during delivery among patients with PCOS were not statistically significant compared with no PCOS on adjusted analysis.

In Data S1, after further adjusting for preeclampsia and eclampsia, PCOS still remained independently associated with increased odds of aforementioned cardiovascular complications of peripartum cardiomyopathy, heart failure, pulmonary edema, acute kidney injury, cardiac arrhythmia, and venous thromboembolism (Table S3).

A supplementary analysis after incorporating missing values mirrored the primary analysis, by showing increase odds of cardiovascular complications with PCOS, except for acute coronary syndrome and stroke (Table S4).

Predictors of Preeclampsia in Patients with PCOS

Among women with PCOS, the factors of older age (>35 years), Black race, diabetes, dyslipidemia, chronic hypertension, and obesity were identified as independent predictors of preeclampsia. When compared with patients with PCOS in the lowest quartile of income, women with PCOS in the higher median income groups had lower odds of developing preeclampsia. Moreover, patients with PCOS with private insurance as their primary payer had lower odds of developing preeclampsia when compared with Medicare patients (Figure 6).

DISCUSSION

Key Findings

Our large contemporary, real-world population study, including 71 million delivery hospitalizations in the United States, yielded the following principal findings: (1) A history of PCOS is independently associated with higher cardiovascular complications during delivery hospitalizations, including the development of preeclampsia, eclampsia, peripartum cardiomyopathy, heart failure, pulmonary edema, cardiac

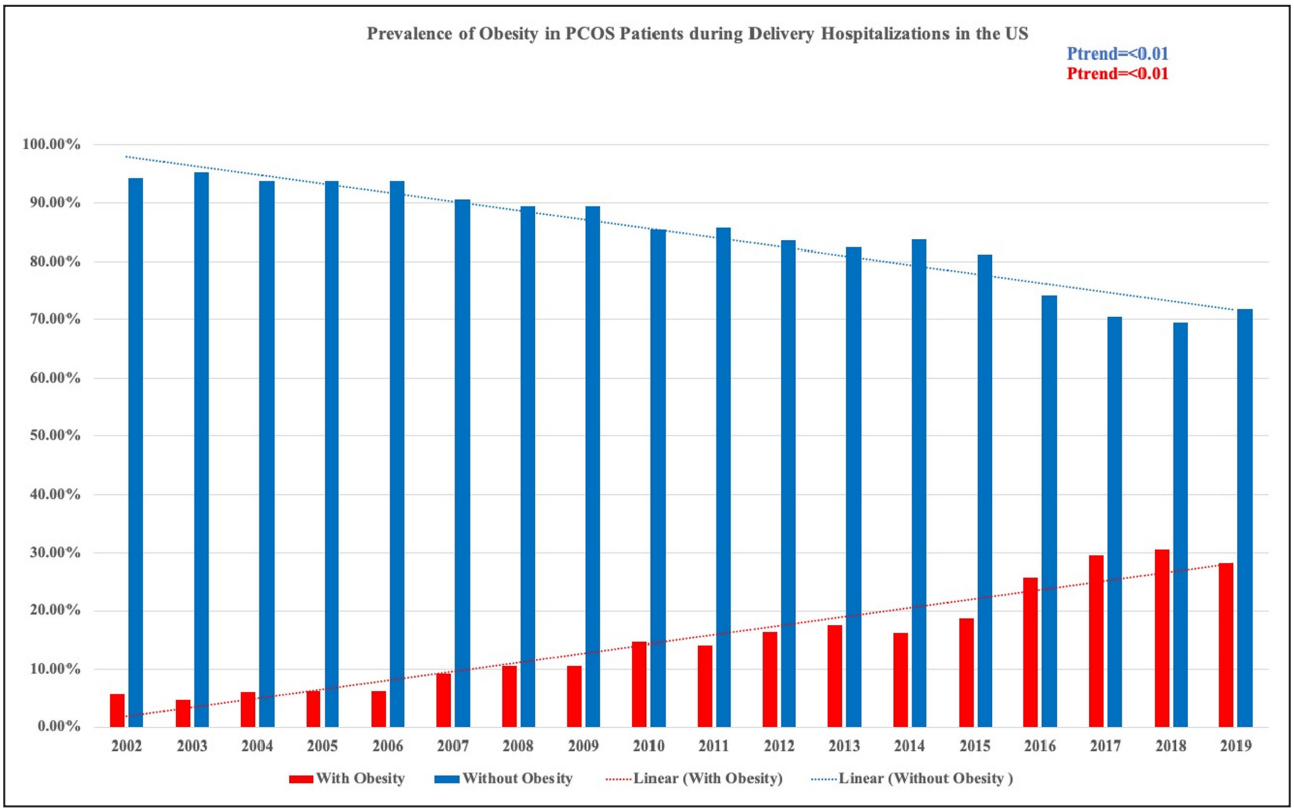

Figure 4. Trend of prevalence of obesity during delivery hospitalizations.
PCOS indicates polycystic ovary syndrome.

arrhythmias, and venous thromboembolism. (2) A diagnosis of PCOS during delivery hospitalization is associated with increased cost and length of delivery hospitalizations. (3) Prevalence of PCOS and obesity during delivery hospitalizations is increasing in the United States over a 17-year period. (4) Age of >35 years, Black race, diabetes, dyslipidemia, chronic hypertension, and obesity were identified as independent predictors of preeclampsia in patients with PCOS. Moreover, patients with PCOS in the highest quartile of income and with private insurances had lower odds of developing preeclampsia.

Table 2. Complication Rates (per 100 000 Delivery Hospitalizations) and Hospital Resource Use in Patients With and Without PCOS

Variables	No PCOS (71 240 633)	PCOS (195 675)	*P* value
Preeclampsia	4353	10 255	<0.01
Eclampsia	134	348	<0.01
Peripartum cardiomyopathy	30	81	<0.01
Heart failure	44	103	<0.01
Acute kidney injury	50	123	<0.01
Acute coronary syndrome	<11*	<11*	0.12
Stroke	33	51	0.16
Pulmonary edema	38	111	<0.01
Cardiac arrhythmias	483	1407	<0.01
Venous thromboembolism	34	89	<0.01
Length of stay, mean (IQR), d	2 (2–3)	3 (2–4)	<0.01
Cost of hospitalization, mean (IQR), $	3616 (2520–5274)	4901 (3423–7175)	<0.01

Results presented as number, unless otherwise indicated. IQR indicates interquartile range; and PCOS, polycystic ovarian syndrome.
*Cells with count <11 are not reportable, per Healthcare Cost and Utilization Project guidelines.

PCOS and Risk for CVD

First, our study found PCOS is an independent predictor of acute adverse cardiovascular complications at the time of delivery hospitalization. Our work builds on prior investigation in this area. Previously, using a retrospective cohort of US insurance claims, Alur-Gupta et al performed an analysis of 42 000 women with PCOS and reported an increased risk of preeclampsia and cardiovascular complications in the postpartum period.[16] Another meta-analysis found that women with PCOS had a 3.5-fold increased risk of developing preeclampsia.[15] Our study reaffirms a heightened risk of preeclampsia in women with PCOS and extends prior work by documenting an excess risk of diverse peripartum cardiovascular complications in this high-risk population. We used a large nationally representative

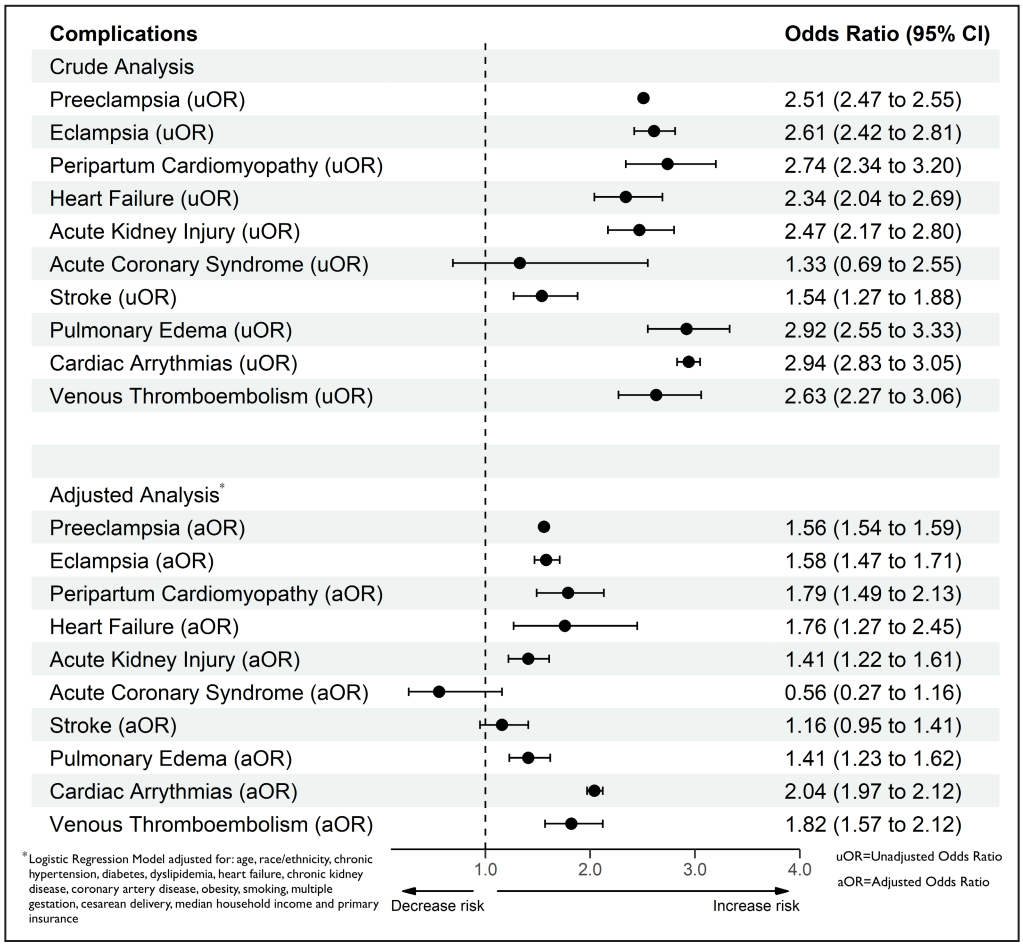

Figure 5. Adjusted odds ratios (aORs) and unadjusted odds ratios (uORs) for in-hospital complications.

sample of nearly 200 000 women with PCOS at delivery and tracked trends in PCOS prevalence at delivery over a 17-year period.

Furthermore, PCOS has been associated with an increased risk of future CVD[1]; however, whether this association with long-term cardiovascular risk is independent of coexisting CVD risk factors, such as obesity, has been conflicting. Some studies,[11–13,23,24] but not all,[25] have suggested an independent association. The association of PCOS with future CVD risk may be stronger among women of reproductive age, but not for women who have already transitioned to menopause.[12] Our study adds to the existing literature for women of reproductive age by reporting that PCOS remains a significant predictor of acute cardiovascular complications during delivery hospitalizations, even after adjustment of obesity, diabetes, dyslipidemias, and age. In addition, our study reports the novel finding of higher mean length of hospital stay along with higher mean hospitalization cost associated with delivery hospitalizations associated with a PCOS diagnosis. We postulate that increased hospital resource use is also a surrogate for the greater rates of adverse cardiovascular events during the hospitalization. Moreover, PCOS complications are a source of significant economic burden on the health care system.[26,27] For example, one report estimated that treating PCOS cost a total of $8 billion worldwide and $4.3 billion in the United States, even after excluding treatment for its long-term complications.[28]

Adverse Trends in PCOS and PCOS-Associated Complications

Second, we report adverse trends in PCOS and PCOS-associated complications, which are observed in the context of concerning population-level trends in cardiometabolic health among reproductive-aged women. In recent decades, the increase in PCOS coincided with the increased prevalence of obesity from 28.4% to 55.8% in US women of reproductive age.[29] Our study findings overall agree with prior reported literature that suggests that cardiovascular risk factors during pregnancy are increasing.[30] For instance,

Subgroup	without Preeclampsia	with Preeclampsia	OR (95% CI)
All Patients	175608	20067	
Age			
<35yr (Reference)	138976(79.1)	15160(75.5)	
>35yr	36631(20.9)	4908(24.5)	1.06 (1.02 to 1.10)
Race			
Caucasians (Reference)	109191(62.2)	12268(61.1)	
African Americans	14102(8.0)	2256(11.2)	1.16 (1.10 to 1.22)
Hispanics	18320(10.4)	2209(11.0)	0.98 (0.93 to 1.03)
Asian or Pacific Islander	11099(6.3)	902(4.5)	0.80 (0.75 to 0.86)
Native American	860(0.5)	118(0.6)	1.16 (0.95 to 1.42)
Others	6057(3.4)	635(3.2)	0.96 (0.88 to 1.05)
Chronic Hypertension			
No (Reference)	174239(99.2)	17974(89.6)	
Yes	1369(0.8)	2093(10.4)	13.83 (12.85 to 14.89)
Diabetes			
No (Reference)	153076(87.2)	15681(78.1)	
Yes	22532(12.8)	4386(21.9)	1.52 (1.46 to 1.58)
Dyslipidemias			
No (Reference)	172012(98.0)	19330(96.3)	
Yes	3596(2.0)	737(3.7)	1.37 (1.26 to 1.50)
Congestive Heart Failure			
No (Reference)	175475(99.9)	19954(99.4)	
Yes	133(0.1)	114(0.6)	3.75 (2.75 to 5.09)
Chronic Kidney Disease			
No (Reference)	175578(100.0)	20037(99.9)	
Yes	30(0.0)	30(0.1)	0.98 (0.52 to 1.86)
Coronary Artery Disease			
No (Reference)	175524(100.0)	20047(99.9)	
Yes	84(0.0)	20(0.1)	0.69 (0.39 to 1.21)
Obesity			
No (Reference)	140427(80.0)	13282(66.2)	
Yes	35181(20.0)	6785(33.8)	1.77 (1.72 to 1.83)
Smoking			
No (Reference)	172078(98.0)	19568(97.5)	
Yes	3530(2.0)	499(2.5)	1.07 (0.97 to 1.18)
Multiple Gestation			
No (Reference)	69899179(98.1)	184622(94.4)	
Yes	1341454(1.9)	11053(5.6)	1.80 (1.70 to 1.90)
Cesarean delivery			
No (Reference)	49128622(69.0)	105619(54.0)	
Yes	22112011(31.0)	90056(46.0)	2.37 (2.29 to 2.44)
Median Household Income			
0-25th percentile (Reference)	30861(17.6)	4404(21.9)	
26-50th percentile	40355(23.0)	5009(25.0)	0.93 (0.89 to 0.97)
51-75th percentile	49884(28.4)	5570(27.8)	0.88 (0.84 to 0.92)
76-100th percentile	53050(30.2)	4894(24.4)	0.77 (0.73 to 0.81)
Primary payer			
Medicare (Reference)	1383(0.8)	253(1.3)	
Medicaid	32009(18.2)	4419(22.0)	0.94 (0.80 to 1.09)
Private insurance	134545(76.6)	14521(72.4)	0.83 (0.71 to 0.96)
Self-Pay	1961(1.1)	180(0.9)	0.79 (0.64 to 0.98)
No Charge	72(0.0)	5(0.0)	0.30 (0.11 to 0.81)
others	5369(3.1)	645(3.2)	0.93 (0.78 to 1.10)

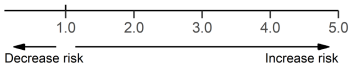

Figure 6. Predictors of preeclampsia in patients with polycystic ovary syndrome.
In Subgroup Race, "others" depicts other race/ethnicities not listed or multiracial. OR indicates odds ratio.

Bornstein and colleagues' analysis of the Centers for Disease Control and Prevention natality database from 1989 to 2018 revealed that there has been a >200% increase in CVD risk factors in pregnant US women during the study period.[31] Our study adds to the existing literature by showing that similar trends of PCOS and obesity have also been observed from 2002 to 2019 at delivery hospitalization.

Moreover, this deterioration in the health of reproductive-aged women may lead to further worsening of maternal cardiovascular and obstetric morbidity and mortality rates as well as poor neonatal outcomes. Prior studies have also found that poorer maternal cardiovascular health is associated with poorer cardiovascular health of their offspring.[32] Thus, optimizing the cardiovascular health of women with PCOS before, during, and after pregnancy is crucial. In this context, it is recommended by the international PCOS guidelines to routinely evaluate women with PCOS for CVD risk by checking body weight, blood pressure, fasting blood glucose, and oral glucose tolerance test. In the context of uncertainty about cardiovascular risk status, the coronary artery calcium score may be considered for women aged >40 years to refine risk stratification and guide shared decision making about preventive pharmacotherapies.[1,4,17,33,34] Lifestyle modifications remain the first treatment given the beneficial effect of weight loss on cardiometabolic profile.[35] Furthermore, in addition to lifestyle modifications, metformin is recommended for women with PCOS who have impaired glucose tolerance tests.[36] More recently, sodium-glucose cotransport-2 inhibitors and glucagon-like peptide-1 receptor agonists have shown promise in the treatment of PCOS-associated cardiometabolic risk.[37,38]

Disparities in PCOS and Adverse PCOS-Associated Outcomes

Third, our study reports predictors of the development of preeclampsia in patients with a history of PCOS from a large population sample. Advanced age, Black race, obesity, and dyslipidemia are some of the expected predictors of preeclampsia that have been described by previous studies.[19,39–42] Our large population-based study further confirms that these demographic and CVD risk factors during pregnancy are also independent predictors of preeclampsia in patients with PCOS. The prevalence of PCOS was found to be lower among Black women, which may be attributable to underdiagnosis or underreporting; however, among women with PCOS, Black women were at greater risk for preeclampsia. Structural racism, disparities in access to health care services, and other social determinants of health are likely contributing to the poorer outcomes among Black women.[42,43] There are significant racial disparities in reduced access to menstrual counseling and obstetrics/gynecologic services, which is a driver of adverse events among Black women.[44]

Socioeconomic Factors and PCOS Complications

Fourth, our study additionally suggests that socioeconomic factors may be independent predictors of adverse outcomes at delivery among women with PCOS. For instance, women with PCOS in the higher-income quartiles had lower odds of developing preeclampsia compared with low-income women with PCOS. Moreover, admissions among women with primary private insurance, as opposed to Medicare patients, had lower odds of developing preeclampsia. Previous literature has outlined the influence of social determinants of health on CVD risk,[42] and that higher socioeconomic status is associated with more favorable health status and greater use of CVD preventive services.[43]

Study Strengths and Limitations

Our study findings should be considered in the context of several important limitations. NIS is an administrative claim-based database that uses *ICD-9* and *ICD-10* codes for diagnosis; although we have used diagnosis codes less prone to error, coding errors cannot be excluded. One known limitation of administrative database research is that misclassification bias can occur from use of *ICD-9* and *ICD-10* diagnostic codes which may imperfectly classify the condition being studied. For example, O14.2 "HELLP" syndrome can occur in either preeclampsia or eclampsia. We were not able to include important variables, such as gestational age at delivery, history of preeclampsia/eclampsia, prepregnancy body mass index, or history of infertility treatment, in our regression model because of a lack of specific *ICD* codes for these diagnoses. There was a change in the method of NIS to improve national estimates in 2012 and a change in coding practices from *ICD-9* to *ICD-10* in quarter 4 of 2015; however, it did not affect disease prevalence after 2012 or 2015.[20] Trends in the prevalence of obesity and PCOS over time may be attributable to better capturing of these diagnoses over time by *ICD* coding or attributable to increased awareness about PCOS. Undercoding of PCOS and comorbidities like obesity remains a concern, as noted by previous studies.[16,45] However, we compared our study findings with Swedish Medical Birth registry analysis using same *ICD-9* and *ICD-10* codes as our study, and patients who also reported a prevalence of 0.3%.[46] Furthermore, we used *ICD* codes that have been validated by a prior study.[47] Another limitation is that NIS collects data on inpatient discharges, and each admission is registered as an independent event. NIS samples are not designed to follow up patients

longitudinally, so long-term outcomes could not be assessed from the present data set. Only information at time of hospital delivery was available for analysis. In addition, like any observational study, association does not mean causation and conclusions should be drawn cautiously.

Despite these limitations, our study has many strengths, such as including a large multiethnic sample nationally representative of the US delivery population, which allowed us to have sufficient statistical power to examine cardiovascular complications associated with deliveries among women with PCOS, as well as 17-year trends in prevalence of PCOS at time of delivery, length of stay, and hospitalization costs. Although the overall rate of cardiovascular complications was low, our data indicate an increased CVD burden in patients with PCOS that might extend beyond the delivery hospitalization and call for closer surveillance of this at-risk group. We hope that these findings garner further study in this area, including investigation on how best to mitigate cardiovascular and pregnancy-associated risks among women with PCOS.

CONCLUSIONS

In conclusion, we report higher cardiovascular complication rates, including preeclampsia, eclampsia, peripartum cardiomyopathy, heart failure, cardiac arrhythmia, and venous thromboembolic disease, among women with PCOS, compared with those without PCOS, during delivery hospitalizations in the United States over a 17-year period. Moreover, there is a trend of increasing prevalence of PCOS and obesity in the United States during delivery hospitalizations. Furthermore, we report predictors of preeclampsia with PCOS, including advanced maternal age, Black race, obesity, diabetes, chronic hypertension, and dyslipidemia. We also report that higher quartile of income and private insurance is associated with decreased risk of preeclampsia. Delivery hospitalizations in women with PCOS, compared with patients without PCOS, are associated with increased length and cost of hospitalization. Further focused studies are needed to elucidate the optimal prevention and management strategies for women with PCOS to mitigate the short- and long-term pregnancy-associated cardiovascular complications.

ARTICLE INFORMATION

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Disclosures

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Supplemental Material

Data S1
Tables S1–S4

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

List of variables used in logistic regression analysis to compute adjusted odds of in-hospital complications

1- Age
2- Race
3- Chronic Hypertension
4- Diabetes
5- Dyslipidemia
6- Congestive Heart Failure
7- Chronic Kidney Disease
8- Coronary Artery Disease
9- Obesity
10- Smoking
11- Multiple Gestation
12- Cesarean Delivery
13- Median Household Income
14- Primary Insurance

List of variables used in logistic regression analysis to compute independent predictors of preeclampsia in patients with PCOS

1- Age
2- Race
3- Chronic Hypertension
4- Diabetes
5- Dyslipidemia
6- Congestive Heart Failure
7- Chronic Kidney Disease
8- Coronary Artery Disease
9- Obesity
10- Smoking
11- Multiple Gestation
12- Cesarean Delivery
13- Median Household Income
14- Primary Insurance

Table S1. ICD Procedure and Diagnosis codes used.

Variables	ICD-10	ICD-9
PCOS	E282	256.4
Preeclampsia	O1400, O140, O1402, O1403, O1404, O1405, O1490, O1492, O1493, O1494, O1495, O149, O141, O1410, O1412, O1413, O1414, O1415, O11, O111, O112, O113, O114, O115, O119	64241, 64242, 64243, 64244, 64250, 64251, 64252, 64253, 64254, 64270, 64271, 64272, 64273, 64274
Eclampsia	O142, O1420, O1422, O1423, O1424, O1425, O15, O150, O1500, O1502, O1503, O151, O152, O159	64260, 64261, 64262, 64263, 64264
Delivery	10D0, 10E0, O60, O61, O62, O63, O64, O65, O66, O67, O68, O69, O70, O71, O72, O73, O74, O75, O76, O77, O80, O82, Z37, Z38	72, 73,75, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 662, 663, 664, 665, 666, 667, 668, 669, V27
Peripartum Cardiomyopathy	O903	6745
Heart Failure	I5021, I5031, I5033, I5041, I5043	42821, 42823, 42831, 42841, 42843
Acute Kidney Injury	N17	584,
Acute Coronary Artery Disease	I2101, I2102, I2109, I211, I2119, I2111, I212, I2129, I213, I214, I219	41000, 41001, 41002, 41010, 41011, 41012, 41020, 41021, 41022, 41030, 41031, 41032, 41040, 41041, 41042, 41050, 41051, 41052, 41060, 41061, 41062, 41080, 41081, 41082, 41090, 41091, 41092

Stroke	I60, I61, I62, I63, I650, I688, O873, O2250, O2251, O2252	430, 431, 432, 433, 437, 6715
Pulmonary edema	J810, J811, I501	514
Cardiac Arrhythmias	Z450, Z950, T821, R001, R008, R000, I459, I456, I441, I442, I443, I47, I48, I49	4260, 42613, 4267, 4269, 42610, 42612, 4270, 4271, 4272, 4273, 4274, 4276, 4277, 4278, 4279, 7850, 99601, 99604, V450, V533
Venous Thromboembolism	I82	453

ICD: International Classification of Diseases

Table S2. Odds of cardiovascular and other complications in patients with PCOS vs no PCOS.

Variables	uOR	aOR	p-value
Preeclampsia	2.51 (2.47-2.55)	1.56 (1.54-1.59)	<0.01
Eclampsia	2.61 (2.42-2.81)	1.58 (1.47-1.71)	<0.01
Peripartum Cardiomyopathy	2.74 (2.34-3.20)	1.79 (1.49-2.13)	<0.01
Heart Failure	2.34 (2.04-2.69)	1.76 (1.27-2.45)	<0.01
Acute Kidney Injury	2.47 (2.17-2.80)	1.41 (1.22-1.61)	<0.01
Acute Coronary Syndrome	1.33 (0.69-2.55)	0.56 (0.27-1.16)	0.12
Stroke	1.54 (1.27-1.88)	1.16 (0.95-1.41)	0.16
Pulmonary Edema	2.92 (2.55-3.33)	1.41 (1.23-1.62)	<0.01
Cardiac Arrhythmias	2.94 (2.83-3.05)	2.04 (1.97-2.12)	<0.01
Venous Thromboembolism	2.63 (2.27-3.06)	1.82 (1.57-2.12)	<0.01

IQR: Interquartile Range, PCOS: Polycystic Ovary Syndrome, uOR: Unadjusted Odds Ration, aOR: Adjusted Odds Ratio
Adjusted for age, race/ethnicity, chronic hypertension, diabetes, dyslipidemia, heart failure, chronic kidney disease, coronary artery disease, obesity, smoking, multiple gestation, Cesarean delivery, median household income and primary insurance.

Table S3. Adjusted predictors of cardiovascular complications among women with PCOS adjusted for preeclampsia and eclampsia.

Variables	aOR	p-value
Peripartum Cardiomyopathy	1.55 (1.29-1.87)	<0.01
Heart Failure	1.51 (1.12-2.03)	<0.01
Acute Kidney Injury	1.15 (1.01-1.31)	0.04
Acute Coronary Syndrome	0.48 (0.23-1.00)	0.05
Stroke	0.99 (0.81-1.21)	0.94
Pulmonary Edema	1.15 (1.01-1.32)	<0.01
Cardiac Arrhythmias	1.98 (1.90-2.06)	<0.01
Venous Thromboembolism	1.68 (1.43-1.97)	<0.01

aOR: Adjusted Odds Ratio; PCOS: Polycystic Ovary Syndrome
Adjusted for age, race/ethnicity, chronic hypertension, diabetes, dyslipidemia, heart failure, chronic kidney disease, coronary artery disease, obesity, smoking, multiple gestation, Cesarean delivery, median household income and primary insurance plus additional adjustment for preeclampsia and eclampsia.

Table S4. Adjusted predictors of cardiovascular complications among women with PCOS after including missing values in the logistic regression analysis.

Variables	aOR	p-value
Preeclampsia	1.74(1.71-1.77)	<0.01
Eclampsia	1.68(1.56-1.81)	<0.01
Peripartum Cardiomyopathy	1.66(1.38-2.00)	<0.01
Heart Failure	1.74(1.25-2.42)	<0.01
Acute Kidney Injury	1.43(1.25-1.64)	<0.01
Acute Coronary Syndrome	0.57(0.28-1.16)	0.12
Stroke	1.17(0.96-1.43)	0.12
Pulmonary Edema	1.51(1.32-1.73)	<0.01
Cardiac Arrhythmias	2.14(2.06-2.20)	<0.01
Venous Thromboembolism	1.88(1.61-2.18)	<0.01

aOR: Adjusted Odds Ratio; PCOS: Polycystic Ovary Syndrome
Adjusted for age, race/ethnicity, chronic hypertension, diabetes, dyslipidemia, heart failure, chronic kidney disease, coronary artery disease, obesity, smoking, multiple gestation, Cesarean delivery, median household income and primary insurance