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ORIGINAL RESEARCH

In-Hospital Complications in Pregnancies Conceived by Assisted Reproductive Technology

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BACKGROUND: Assisted reproductive technology (ART) has emerged as a common treatment option for infertility, a problem that affects an estimated 48 million couples worldwide. Advancing maternal age with increasing prepregnancy cardiovascular risk factors, such as chronic hypertension, obesity, and diabetes, has raised concerns about pregnancy complications associated with ART. However, in-hospital complications following pregnancies conceived by ART are poorly described.

METHODS AND RESULTS: To assess the patient characteristics, obstetric outcomes, vascular complications and temporal trends of pregnancies conceived by ART, we analyzed hospital deliveries conceived with or without ART between January 1, 2008, and December 31, 2016, from the United States National Inpatient Sample database. We included 106 248 deliveries conceived with ART and 34 167 246 deliveries conceived without ART. Women who conceived with ART were older (35 versus 28 years; $P<0.0001$) and had more comorbidities. ART-conceived pregnancies were independently associated with vascular complications (acute kidney injury: adjusted odds ratio [aOR], 2.52; 95% CI 1.99–3.19; and arrhythmia: aOR, 1.65; 95% CI, 1.46–1.86), and adverse obstetric outcomes (placental abruption: aOR, 1.57; 95% CI, 1.41–1.74; cesarean delivery: aOR, 1.38; 95% CI, 1.33–1.43; and preterm birth: aOR, 1.26; 95% CI, 1.20–1.32), including in subgroups without cardiovascular disease risk factors or without multifetal pregnancies. Higher hospital charges ($18 705 versus $11 983; $P<0.0001$) were incurred compared with women who conceived without ART.

CONCLUSIONS: Pregnancies conceived by ART have higher risks of adverse obstetric outcomes and vascular complications compared with spontaneous conception. Clinicians should have detailed discussions on the associated complications of ART in women during prepregnancy counseling.

Key Words: cardiovascular disease risk factors ■ in vitro fertilization ■ pregnancy ■ prevention

Infertility, defined as the inability to conceive within 1 year of unprotected intercourse,[1] affects an estimated 48 million couples worldwide[2] and ≈15% of women of reproductive age in the United States.[3] The common causes of female infertility include ovulatory dysfunction, fallopian tubal disease, pelvic adhesions, and endometriosis.[4] Assisted reproductive technology (ART) is a group of medical procedures for treating infertility, which includes medication to control timing of ovulation, as well as procedures such as in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI). To date, ART has contributed to the birth of more than 5 million infants worldwide.[5]

In 2019, there were ≈275 million women diagnosed with cardiovascular disease (CVD) worldwide,[6] which caused 35% of total female deaths.[7] While CVD is the leading cause of maternal mortality in the United States,[8] studies regarding the association between

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CLINICAL PERSPECTIVE

What Is New?

- Our analysis is the first population-based study and the largest analysis to consider both obstetric outcomes and vascular complications at time of delivery in women who conceived with assisted reproductive technology, where we showed that pregnancies conceived with assisted reproductive technology are independently associated with 1.7- and 2.5-fold increased risks for arrhythmia and acute kidney injury, respectively, even after adjusting for baseline risk profile.

What Are the Clinical Implications?

- Primary and specialist care clinicians should counsel women that assisted reproductive technology carries a higher risk of obstetric and vascular complications which will require close monitoring, particularly during delivery.
- While our study did not explore the relationship between assisted reproductive technology and long-term cardiovascular disease, there is growing understanding that additive adverse effects of infertility may have implications on long-term cardiovascular risks through shared pathogenesis and vascular dysfunction.

Nonstandard Abbreviations and Acronyms

ART	assisted reproductive technology
ICSI	intracytoplasmic sperm injection
NIS	National Inpatient Sample

ART and future maternal CVD are limited with inconsistent findings. Although a meta-analysis concluded that ART treatment does not increase risk of overall cardiac events, only 6 studies were included.[9] Advancing maternal age with increasing prepregnancy cardiovascular risk factors, such as chronic hypertension, obesity, and diabetes, has raised concerns about the pregnancy complications associated with ART. Adverse pregnancy outcomes, such as preeclampsia, have now been established as risk factors for future CVD.[10]

Given the multimorbidity associated with women undergoing ART, understanding their risks of adverse obstetric and vascular outcomes may help to guide postpartum vascular risk reduction strategies. Because of the paucity of population-based data on vascular complications such as arrhythmia and ischemic stroke, we aimed to assess the patient characteristics, obstetric outcomes, vascular complications, and temporal trends in pregnancies conceived by ART using a nationally representative database.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Source

Data from the US National Inpatient Sample (NIS) database containing hospital discharges between January 1, 2008, and December 31, 2016, was used in this study. The NIS is the largest, all-payer inpatient health care database in the United States, developed by the Agency for Healthcare Research and Quality within their Healthcare Cost and Utilization Project. The NIS contains data on ≈20% stratified samples of all discharges from US hospitals, which is equivalent to 7 to 8 million hospital discharges per annum. This study involved the analysis of deidentified data and was exempt from institutional review board approval.

Study Population

We included all women admitted for delivery using a validated algorithm.[11] Briefly, *International Classification of Diseases, Ninth Revision* and *Tenth Revision, Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*) obstetric diagnosis codes were used to identify delivery hospitalization episodes (Table S1A). For the exposure of ART, we extracted records with an ART code (Table S1A). For outcomes, we extracted information on selected vascular complications (acute kidney injury, arrhythmia, ischemic stroke, peripartum cardiomyopathy, venous thromboembolism) and obstetric outcomes (cesarean delivery, placental abruption, preterm birth; Table S1B), as well as cost outcomes (length of stay and total billed hospitalization charge). In addition, we extracted covariate information on demographics and comorbidities (Table S1C). The *ICD-9-CM* and *ICD-10-CM* codes are included in Table S1. In the temporal analyses, we grouped the years as follows: 2008 to 2010, 2011 to 2013, and 2014 to 2016. We performed 2 stratified analyses in the ART and non-ART groups: presence versus absence of CVD risk factors, and singleton versus multifetal pregnancies.

Statistical Analysis

The NIS includes sampling weights that can be used to calculate national estimates and correct variances.[12] During the study period, there was a change in the sampling design in 2012, from using all discharges from a sample of hospitals, to using a sample of discharges from all hospitals participating in the Healthcare Cost and Utilization Project. To ensure compatible data

across the study period, we applied a discharge trend weight provided by the Agency for Healthcare Research and Quality in all our analyses. We applied the NIS population survey weights (*svy* prefix in Stata; StataCorp, College Station, TX) to all analyses as per Agency for Healthcare Research and Quality recommendations to decrease error margin of the national estimates and provide more stable estimates.

We created a missing category for missing data in the race and ethnicity, and median ZIP code income variables because of the large number of missing data, so we could perform sensitivity analyses to assess the effect of excluding observations with missing data. For variables with <2% missing data overall, hospitalization episodes with missing data were removed and assumed to be missing at random.

Stata/MP version 14.0 statistical package was used to conduct all analyses. Continuous variables are shown as median and interquartile range, while categorical data are shown as numbers and percentages. To determine statistical difference between the groups for categorical and continuous variables, chi-square and *t* tests were used, respectively. The "nptrend" package was used for trend across ordered groups. Binary logistic regression analyses were used to assess the association of ART with maternal and obstetric outcomes. We adjusted for the following potential confounders: age, median ZIP code income quartile, primary payer, race and ethnicity, weekday admission, year of admission, and comorbidities associated with CVD (chronic kidney disease, congenital heart disease, congestive heart failure, depression, diabetes, dyslipidemia, hypertension, multifetal pregnancy, obesity, preeclampsia/eclampsia, previous myocardial infarction, previous transient ischemic attack or stroke, smoker, valvular disease). The odds ratios are shown with the corresponding 95% CIs.

In addition, we performed nearest neighbor propensity score matching on race and ethnicity, age, and cardiovascular risk factors (congenital heart disease, smoking, previous myocardial infarction, previous stroke, dyslipidemia, valvular disease, depression, diabetes, chronic kidney disease, obesity, congestive heart failure) using the psmatch2 command in Stata. The effect estimate was generated from logistic regression analysis in the matched cohort. An extension of the strengthening the reporting of observational studies in epidemiology checklist, the reporting of studies conducted using observational routinely-collected health data checklist, is shown in Table S2 to summarize our study.[2,13]

RESULTS

Demographic and Patient Characteristics

Our study population included 7 236 075, which were weighted to represent 34 273 494 delivery hospitalization episodes between 2008 and 2016 (Figure 1). The percentage of delivery episodes from ART increased over time from 0.05% in 2008 to 0.51% in 2016 (P_{trend}<0.0001; Figure S1). We stratified our study population according to use of ART for conception, which consisted of 0.31% (weighted n=106 248) with ART and 99.69% (weighted n=34 167 246) without ART (Table 1). Women who conceived by ART were older (median age 35 versus 28 years; *P*<0.0001), had higher proportion of White women (66.13% versus 47.82%; *P*<0.0001), and had more women residing in the wealthiest quartile of household income (54.63% versus 21.42%; *P*<0.0001), compared with non-ART (Table 1).

Adverse Pregnancy and Obstetric Outcomes

Women who conceived by ART had a higher prevalence of multifetal pregnancy (28.70% versus 1.95%; *P*<0.0001) and current preeclampsia/eclampsia (10.33% versus 4.42%; *P*<0.0001; Table 1). Over the 9-year study period, the prevalence of current preeclampsia/eclampsia increased (P_{trend}=0.005), while multifetal pregnancy decreased (P_{trend}<0.0001), in both ART and non-ART groups (Table S3). Women who conceived with ART had a higher prevalence of cesarean delivery, preterm birth, and placental abruption in comparison with women who conceived without ART (Table 2). Between 2008 and 2016, the prevalence of preterm birth and cesarean delivery decreased (P_{trend}<0.05) in both ART and non-ART groups over time (Table S3). In the univariable and multivariable regression models, women who conceived with ART had increased odds of placental abruption (adjusted odds ratio [aOR], 1.57; 95% CI, 1.41–1.74; *P*<0.0001), cesarean delivery (aOR, 1.38; 95% CI, 1.33–1.43; *P*<0.0001), and preterm birth (aOR, 1.26; 95% CI, 1.20–1.32; *P*<0.0001), compared with women who conceived without ART (Table 3).

We further stratified the groups according to CVD risk (Table S4) and found that the prevalence of adverse obstetric outcomes was higher in women with CVD risk factors compared with their counterparts without CVD risk factors (Table S5). For example, cesarean delivery was prevalent in 68% of women with ART pregnancies and CVD risk factors. In the regression models, after adjusting for demographic data, women with CVD risk factors and conceived with ART had highest risks of adverse obstetric outcomes out of all groups (Table S6). For example, women with ART pregnancies and CVD risks have an 8-fold and 4-fold increased risk for preterm birth and cesarean delivery, respectively, in comparison with women without ART pregnancies or CVD risks.

The ART and non-ART groups were also stratified according to whether women had singleton or multifetal

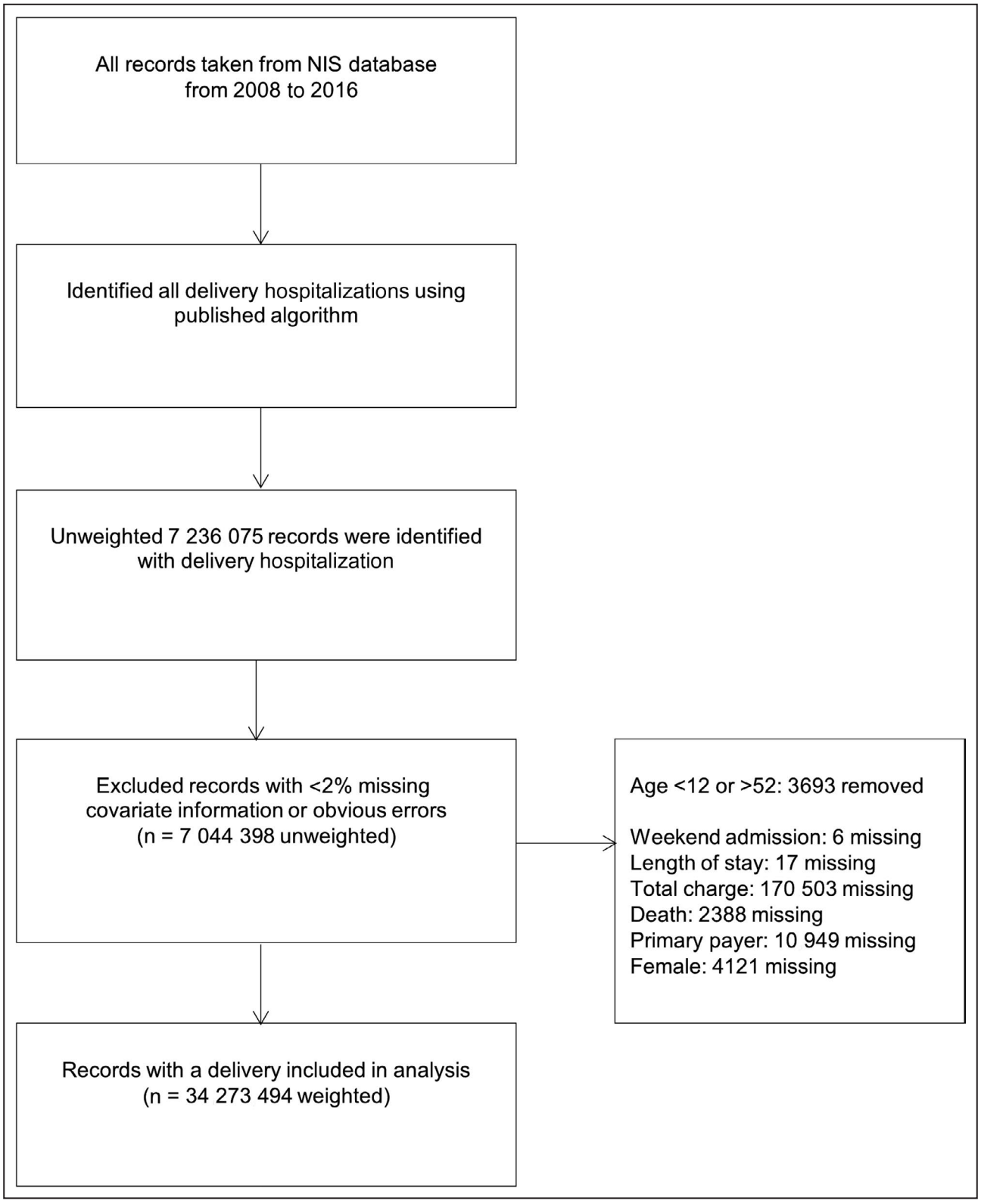

Figure 1. Flow diagram of included/excluded record.

pregnancies (Table S7). For singleton pregnancies, the prevalence of adverse obstetric outcomes remained more common in ART pregnancies. Furthermore, the increased risks of these outcomes also persisted in singleton pregnancies conceived using ART compared with those that were spontaneously conceived

Table 1. Patient Characteristics

Variable	Non-ART	ART	*P* value
Deliveries, %	99.69	0.31	…
Number of deliveries, weighted	34 167 246	106 248	…
Age, y, median (IQR)	28 (23–32)	35 (32–39)	<0.0001*
Race and ethnicity, %			<0.0001*
White	47.82	66.13	
Black	13.16	5.67	
Hispanic	19.28	6.12	
Asian/Pacific Islander	4.67	10.81	
Native American	0.75	0.42	
Other	4.37	4.98	
Missing	9.95	5.87	
Median ZIP code income (quartile)			<0.0001*
First (lowest)	27.69	7.15	
Second	24.93	12.84	
Third	24.28	24.47	
Fourth (highest)	21.42	54.63	
Missing	1.68	0.91	
Weekday admission, %	80.67	82.94	<0.0001*
Length of stay, d, median (IQR)	2 (2–3)	3 (2–4)	<0.0001*
Total charge, $, median (IQR)	11 983 (7937–18 341)	18 705 (11 428–29 968)	<0.0001*
Expected primary payer, %			<0.0001*
Medicare	0.72	0.16	
Medicaid	44.19	4.36	
Private insurance	49.17	91.86	
Self-pay	2.87	1.54	
No charge	0.14	0.02	
Other	2.91	2.06	
Comorbidities, %			
Chronic kidney disease	0.06	0.06	0.96
Congenital heart disease	0.12	0.30	<0.0001*
Congestive heart failure	0.05	0.07	0.18
Current preeclampsia/eclampsia	4.42	10.33	<0.0001*
Depression	2.21	2.88	<0.0001*
Diabetes	1.10	1.16	0.49
Dyslipidemia	0.12	0.42	<0.0001*
Hypertension	2.20	3.67	<0.0001*
Multifetal pregnancy	1.95	28.70	<0.0001*
Obesity	5.52	6.36	0.0002*
Previous MI	0.01	0.01	0.90
Previous TIA/stroke	0.06	0.12	0.0001*
Smoker	7.68	3.66	<0.0001*
Valvular disease	0.28	0.75	<0.0001*

ART indicates assisted reproductive technology; IQR, interquartile range; MI, myocardial infarction; and TIA, transient ischemic attack.
*Denotes statistical significance.

(placental abruption: aOR, 1.86; 95% CI, 1.64–2.12; *P*<0.0001; preterm birth: aOR, 1.57; 95% CI, 1.47–1.68; *P*<0.0001; and cesarean delivery: aOR, 1.44; 95% CI, 1.39–1.50; *P*<0.0001). However, multifetal pregnancies conceived using ART did not have increased risk of placental abruption compared with spontaneously conceived multifetal pregnancies (Figure 2).

Clinical Comorbidities and Vascular Complications

Women who conceived by ART had a higher prevalence of maternal congenital heart disease (0.30% versus 0.12%; *P*<0.0001), dyslipidemia (0.42% versus 0.12%; *P*>0.001), valvular disease (0.75% versus 0.28%; *P*<0.001), and obesity (6.36% versus 5.52%; *P*=0.0002). However, there were more current smokers in the non-ART group compared with the ART group (7.68% versus 3.66%; *P*<0.0001). Over the 9-year study period, the prevalence of maternal dyslipidemia, obesity, and current smokers increased (P_{trend}<0.02), while the prevalence of valvular disease decreased (P_{trend}=0.003) in both ART and non-ART groups (Table S3). Overall, compared with women who conceived without ART, the prevalence of all complications was higher in women who conceived with ART, except for peripartum cardiomyopathy (Table 2). Between 2008 and 2016, the prevalence of acute kidney injury, arrhythmia, and venous thromboembolism increased in the non-ART group but not the ART group over time (P_{trend}<0.001; Table S3). Arrhythmia consisted mainly of sinus node dysfunction and supraventricular tachycardia and did not differ between ART and non-ART groups. Our univariable and multivariable regression models showed that women who conceived with ART had increased odds of acute kidney injury (aOR, 2.52; 95% CI, 1.99–3.19; *P*<0.0001), and arrhythmia (aOR, 1.65; 95% CI, 1.46–1.86; *P*<0.0001), in comparison with women who conceived without ART (Table 3). There was non–statistically significant association, after adjustment, for ischemic stroke, peripartum cardiomyopathy, or venous thromboembolism.

Similar to obstetric outcomes, the prevalence of vascular complications was also found to be higher in women with CVD risk factors, compared with their counterparts without CVD risk factors in both non-ART and ART groups in the stratified analyses (Table S5). These were particularly high in women with ART pregnancies and CVD risk factors. For example, the prevalence of arrhythmia was 174 per 10 000 deliveries. Multivariable modeling showed that women with ART pregnancies and CVD risk factors had the highest risks for acute kidney injury, arrythmia, ischemic stroke, and venous thromboembolism, followed by women with non-ART pregnancies and CVD risk factors, in

Table 2. In-Hospital Obstetric Outcomes and Vascular Complications (per 10 000 Deliveries)

Variable	Non-ART n=34 167 246	ART n=106 248	*P* value
Obstetric outcomes			
Cesarean delivery	3211	5489	<0.0001*
Placental abruption	107	200	<0.0001*
Preterm birth	624	1433	<0.0001*
Vascular complications			
Acute kidney injury	9	38	<0.0001*
Arrhythmia	74	143	<0.0001*
Ischemic stroke	1	3	0.0007*
Peripartum cardiomyopathy	2	3	0.57
Venous thromboembolism	5	12	<0.0001*

ART indicates assisted reproductive technology.
*Denotes statistical significance.

comparison with women with non-ART pregnancies and no CVD risk factors (Table S6). For women with CVD risk factors, the risk of peripartum cardiomyopathy was greater in spontaneous compared with ART-conceived pregnancies.

For singleton pregnancies, the prevalence of vascular complications (acute kidney injury, arrhythmia, ischemic stroke, and venous thromboembolism) remained higher in ART compared with the non-ART group (Table S7). Increased risks of acute kidney injury (singleton: aOR, 2.82; 95% CI, 2.06–3.87; *P*<0.0001; multifetal: aOR, 1.49; 95% CI, 1.05–2.12; *P*<0.0001), and arrhythmia (singleton: aOR, 1.89; 95% CI, 1.62–2.19; *P*<0.0001; multifetal: aOR, 1.32; 95% CI, 1.08–1.62; *P*<0.0001) were also present in ART pregnancies compared with spontaneous conception (Table S8).

Additional sensitivity analyses on complications and outcomes were conducted to examine for the effects of excluding records with missing data (data not shown) and revealed no clinically significant changes in the odds ratios. To account for the baseline differences between the non-ART and ART groups, we repeated our analyses using propensity score matched cohorts based on age, race and ethnicity, and cardiovascular risk factors (Tables S9 and S10). The matched cohort consisted of 6 050 692 (after removal of 993 706 unmatched delivery hospitalizations), which were weighted to represent 29 459 351 delivery hospitalizations, with a good balance of matched variables (Table S11). These supplementary analyses showed similar results to the main analyses.

Financial and Insurance Issues

Women with ART had more weekday admissions (82.94% versus 80.67%; *P*<0.0001), which were mainly paid for by private insurance (91.86% versus 49.17%; *P*<0.0001). For the cost outcomes, the ART group experienced longer peridelivery length of stay (median 3 versus 2 days; *P*<0.0001) and higher hospital charges (median $18 705, interquartile range $11 428–$29 968 versus $11 983, interquartile range $7937-$18 341; *P*<0.0001) in comparison with women without ART (Table 1). These charges increased between 2008 and 2016 in both groups (P_{trend}<0.0001), after adjusting for inflation (Table S3).[14]

DISCUSSION

Our analysis of over 34 million delivery hospitalization episodes is the first population-based study and the largest analysis to consider both obstetric outcomes and vascular complications at time of delivery

Table 3. Association Between Pregnancies Conceived by Assisted Reproductive Techniques and In-Hospital Obstetric Outcomes and Vascular Complications

Variable	Unadjusted*	*P* value	Adjusted†	*P* value
Obstetric outcomes				
Cesarean delivery	2.57 (2.49–2.66)	<0.0001‡	1.38 (1.33–1.43)	<0.0001‡
Placental abruption	1.88 (1.70–2.09)	<0.0001‡	1.57 (1.41–1.74)	<0.0001‡
Preterm birth	2.51 (2.37–2.67)	<0.0001‡	1.26 (1.20–1.32)	<0.0001‡
Vascular complications				
Acute kidney injury	4.37 (3.50–5.46)	<0.0001‡	2.52 (1.99–3.19)	<0.0001‡
Arrhythmia	1.95 (1.72–2.20)	<0.0001‡	1.65 (1.46–1.86)	<0.0001‡
Ischemic stroke	3.67 (1.64–8.20)	0.002‡	2.07 (0.89–4.77)	0.09
Peripartum cardiomyopathy	1.26 (0.57–2.79)	0.57	0.85 (0.30–2.42)	0.76
Venous thromboembolism	2.32 (1.59–3.40)	<0.0001‡	1.36 (0.92–2.00)	0.12

*Data expressed as odds ratios and 95% CIs, reference group is no assisted reproductive technology.
†Adjustment includes age, median ZIP code income quartile, primary payer, race and ethnicity, weekend admission, year of admission, chronic kidney disease, congenital heart disease, congestive heart failure, depression, diabetes, dyslipidemia, hypertension, multifetal pregnancy, obesity, preeclampsia/eclampsia, previous myocardial infarction, previous transient ischemic attack/stroke, smoker, valvular disease.
‡ Denotes statistical significance.

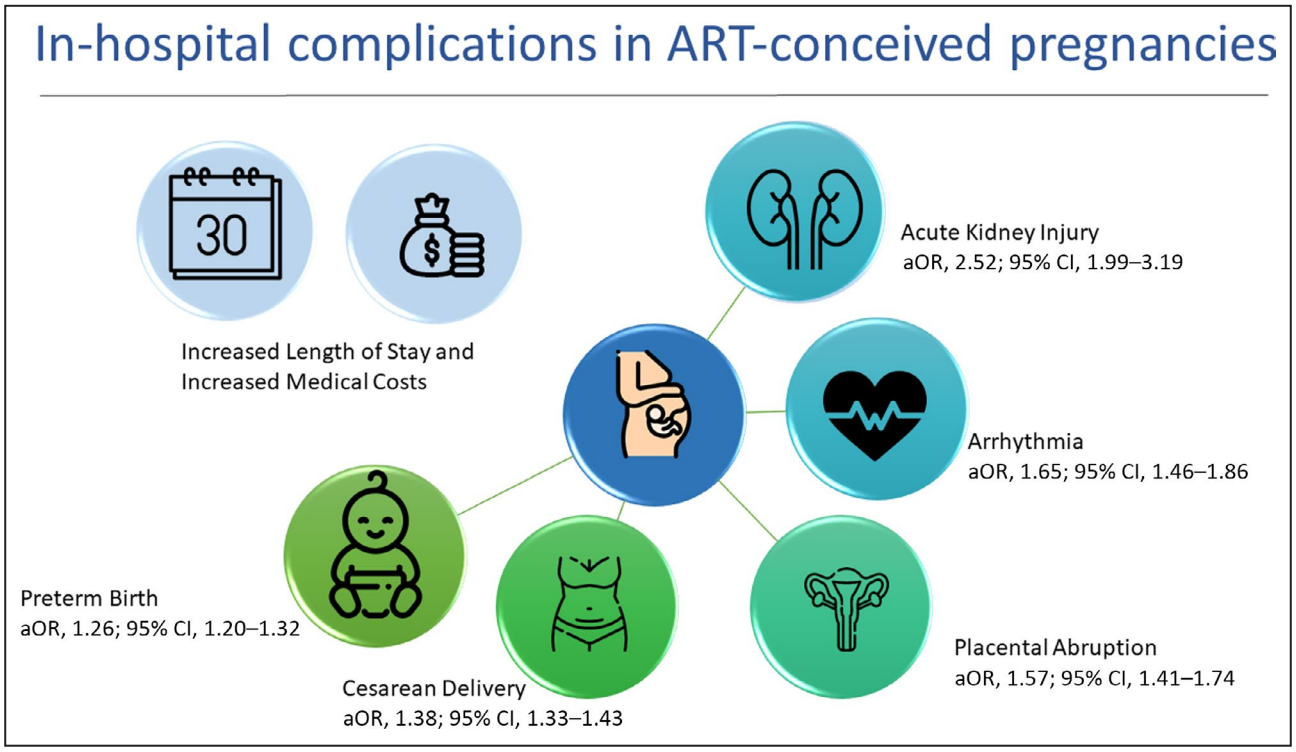

Figure 2. In-hospital complications in assisted reproductive technology–conceived pregnancies.

in women who conceived with ART. We show that the prevalence of pregnancies conceived by ART increased over time, in women who are older and with more comorbidities including dyslipidemia and congenital heart disease. After adjusting for baseline risk profile, ART-conceived pregnancies are independently associated with 1.7- and 2.5-fold risks for arrhythmia and acute kidney injury, respectively. These risks persisted after further stratification into women with and without CVD risk factors, as well as within-subgroup analysis on singleton pregnancies. Although the absolute risk remains low, our study highlights the need for close monitoring of both obstetric and vascular complications during admission for delivery in women who conceived with ART, particularly in those with CVD risk factors.

Comparison With Literature

In keeping with previous smaller studies, our analysis showed increased risks of obstetric outcomes, such as cesarean deliveries and preterm births.[15–19] A single-center cohort study on 650 ART-conceived pregnancies showed that ART was associated with 3.6-fold increased risk of intra- and postpartum serious and potentially life-threatening conditions, including preeclampsia/eclampsia, placental abruption, and maternal cardiovascular dysfunction.[20] An older study using claims data from one health insurance company studied 1 million deliveries, and showed that the odds of severe maternal morbidity, including conditions such as eclampsia, puerperal cerebrovascular disorders, and acute kidney injury, were 1.8 times higher among singleton ART pregnancies compared with non-ART pregnancies during delivery or postpartum readmissions.[21]

We found that there was a large difference in multifetal pregnancies between ART and non-ART groups. This is likely attributable to the practice of placing ≥2 embryos at the time of embryo transfer during the ART procedure. In 2016, the national elective single-embryo transfer rate was only 42.7%.[22] The literature also supports the marked difference we found in the multifetal pregnancy rate between the ART and non-ART groups. The US Centers for Disease Control and Prevention reported that 31.1% of multiple-birth infants were among infants conceived with ART in 2016.[22] The rate of multifetal pregnancy in the United States remained stable at around 2% until the 1970s, with the advent of ART.[23–25]

Potential Mechanisms

In our stratified analysis, women with ART pregnancies and CVD risk factors had increased risks of acute kidney injury, arrhythmia, ischemic stroke, peripartum

cardiomyopathy, and venous thromboembolism, compared with women without ART or CVD risk factors. Derangements in the renin-angiotensin-aldosterone axis and endothelial dysfunction in ART have been suggested to contribute to increased CVD risk.[26] This may be a contributory cause for our finding of increased risk of vascular complications in the ART group. Our study also showed that there is a disproportionate number of women with congenital heart disease seeking ART, who are already at an increased risk of cardiovascular events. Acute changes in maternal hemodynamics attributable to changes in the endogenous hormone levels, including increases in heart rate and decreases in blood pressure, occurs during an IVF cycle, with cardiac functional changes reported in agonist IVF protocols.[27] Furthermore, ovarian hyperstimulation syndrome, a complication of ART, causes an increasingly procoagulant state, severe multiorgan dysfunction, and dramatic fluid shifts within the body.[26] As ART is associated with increased risks of preeclampsia and venous thromboembolism, together with the increased complications of ovarian hyperstimulation syndrome and multifetal gestations arising from ART causing prothrombotic environment and hemodynamic shifts, women who conceived using ART undergo additional circulatory burden. Although multifetal pregnancy acts as a mediator, with ART increasing the risk of multifetal pregnancy that in turn increases the risk of adverse vascular complications, the impact of ART itself is still observed in singleton pregnancy.

Infertility may also act as a confounding factor and contribute to increased cardiovascular risk. For example, thrombophilia and placental disease may cause both infertility and increased cardiovascular risks. Polycystic ovary syndrome, a common cause of female infertility,[28] has been associated with a 7-fold increased risk of myocardial infarction.[29] Similarly, irregular menstrual cycle has been associated with both infertility[30] and increased CVD risk.[31] Furthermore, women with infertility are more likely to have cardiometabolic risk factors, such as atherogenic lipid profile and obesity, compared with fertile women.[32] Nevertheless, it remains challenging to determine whether the increased prevalence of adverse outcomes is attributable to the ART procedure itself[33–36] or maternal factors associated with infertility[37] or is multifactorial.[38–44]

Clinical Implications

Despite CVD being the leading cause of maternal death, the perinatal confidential inquiry report from the United Kingdom showed that many women who died from heart disease during or after pregnancy following ART had preexisting cardiovascular risk factors that were not formally assessed before ART treatment.[45] There is evidence suggesting that lifestyle intervention in women who are obese before infertility treatment may improve cardiometabolic health at 6 months.[46] Therefore, women with cardiac risk factors may benefit from cardiac assessments and screening before ART, in line with recommendations from the perinatal confidential inquiry report.[45,47]

The important clinical implication of our study is how to counsel patients desiring ART, especially those with existing cardiovascular risk factors and regarding long-term cardiovascular implications from ART. While our study did not explore the relationship between ART and long-term CVD, there is growing understanding that additive adverse effects of infertility may have implications on long-term cardiovascular risks through shared pathogenesis and vascular dysfunction.[48] Women should be counseled that ART carries a higher risk of pregnancy complications, which will require close monitoring, particularly during delivery.

Study Strengths

This study has several strengths. First, we examined a large delivery cohort using nationwide data. Second, our study design allowed us to simultaneously examine several important clinical outcomes in a cohort that included both singleton and multifetal pregnancies. Moreover, we also provide type-specific information for women who are already pregnant, in our subgroup analysis of singleton versus multifetal pregnancy. Third, we are the first to evaluate in-hospital cardiovascular complications based on a population cohort. These short-term complications may provide a basis for risk stratification of women at risk of cardiovascular events in the long term.

Study Limitations

Limitations of our study include inherent errors of retrospective database studies, such as exposure misclassification, ascertainment bias, and underreporting of secondary diagnoses. The recording of ART may have improved over time, as a previous study on delivery admissions in the NIS between 2008 and 2011 showed 0.17% prevalence of IVF compared with 0.31% in our study.[49] We were not able to assess all possible confounding factors, for example, the type and number of ART used before conception. Moreover, the NIS does not capture timing of diagnosis or follow-up period over 12 months. As such, we were unable to perform analyses on time to events and duration of infertility or comorbidities. Because of the design of the NIS database, we could assess only hospitalization episodes rather than individual women. Therefore, 1 woman may have multiple delivery hospitalizations during our study period. As our study considers only the delivery population, our results are not generalizable to women who had ART but did not conceive. Because of the lack of drug

information, we could not consider the effect of current or previous pharmacotherapy. Finally, some of the statistically significant results may have been a chance finding since we did not adjust for multiple testing.

In conclusion, women with pregnancies conceived by ART pregnancies are at increased risk of adverse obstetric outcomes and vascular complications, compared with women who conceived spontaneously. Primary and specialist care clinicians should ensure that they communicate these risks and how to mitigate them. Future research should examine the impact of optimization of cardiovascular risk factors before ART on pregnancy complications and long-term cardiovascular health.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S11
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. ICD-9 or ICD-10 codes for conditions studied. (A) Study population. (B) Complications and outcomes. (C) Comorbidities.

A. Study population.

Variables	ICD-9-CM / ICD-9-CM PR codes	ICD-10-CM / ICD-10-PCS codes
Delivery cohort	V27x, 65x, 66x, 720, 721, 7221, 7229, 7231, 7239, 724, 726, 7251, 7252, 7253, 7254, 7271, 7279, 728, 729, 7322, 7359, 736	O601x, O602x, O63x, O64x, O65x, O66x, O68x, O69x, O70x, O74x, O750, O755x, O76x, O77x, O80, O82, Z37x, Z38x, Z390, 10D0x, 10E0x, 0DQR0x, 0DQP0x, 0DQQ0x, 0HQ9Xx, 0KQM0x, 0W8x
Assisted reproductive technology	V2385	O0981x

B. Complications and outcomes.

Complications / outcomes	ICD-9-CM / ICD-9-CM PR codes	ICD-10-CM / ICD-10-PCS codes
Acute kidney injury	584x, 6693x	O904, N170, N171, N172, N178, N179
Arrhythmia	4270x, 4271x, 4272x, 4273x, 4274x, 4276x, 4278x, 4279x	I47x, I48x, I49x
Cesarean delivery	PR 740, 741, 742, 744, 7499	PR 10D00x
Ischemic stroke	43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 43491, 435x, 4358x, 4359x, 436, 4376, 6715, 325	I63x, I693x
Peripartum cardiomyopathy	6745x	O903
Placental abruption	6412x	O450x, O458x, O459x
Preterm birth	64421	O6010X0, O6012X0, O6013X0, O6014X0
Venous thromboembolism	415x, 6732x, 6738x, 4534x	I26x, O882x, O888x, I824x

C. Comorbidities.

Comorbidities	ICD-9-CM codes	ICD-10-CM codes

Cardiac and circulatory congenital anomalies	745x, 746x, 747x, V1365	P293x, Q2x, Z8774
Dyslipidemia	2720-2724	E780x, E781, E782, E783, E784x, E785
Current preeclampsia/eclampsia	6424x, 6425x, 6426x, 6427x	O11x, O14x, O15x,
Multifetal pregnancy	651x, V272-V277	O30x, O31x, Z372-Z377
Previous myocardial infarction	412	I252, I256
Previous transient ischemic attack / stroke	V1254	Z8673
Smoker	3051, 6490x, V1582	F17200, Z87891, O9933x
Selected Elixhauser comorbidities (depression, diabetes (uncomplicated and with chronic complications), heart failure, hypertension, obesity, renal failure, valvular disease)	List of comorbidities and associated ICD-9-CM code can be found (Quan 2005 et al.) at: http://czresearch.com/dropbox/Quan_MedCare_2005v43p1130.pdf	List of comorbidities and associated ICD-10-CM code can be found at: https://hcup-us.ahrq.gov/toolssoftware/comorbidityicd10/Com-ICD10CM-ReferncFile-v2021-1.xlsx

Table S2. The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract: methods section.	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Abstract: methods section.
Introduction					

Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction: paragraph 1 and 2.		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction: last sentence.		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods: study population section.		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods: study population section.		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the	Methods: study population section, Table S1.	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published	Methods: study population section, Table S1.

		sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Table S1.	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Table S1.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Table S1.		

Bias	9	Describe any efforts to address potential sources of bias	Methods: data analysis section.		
Study size	10	Explain how the study size was arrived at	Methods: data source section.		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods: data analysis section.		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed	Methods: data analysis section.		

		Cross-sectional study - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		…		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Methods: data source and data analysis sections.
Linkage		…		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	N/A.
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially	Figure 1.	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.*, study population selection)	Figure 1.

		eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	Table 1.		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Table 2.		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Table 3.		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Tables S3-S11.		
Discussion					

Key results	18	Summarise key results with reference to study objectives	Discussion: first paragraph.		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion: study limitations section.	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Discussion: study limitations section.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion: final paragraph.		
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion: clinical implications.		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable,	Sources of funding section.		

		for the original study on which the present article is based			
Accessibility of protocol, raw data, and programming code		…		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Supplemental materials.

Table S3. Patient characteristics, comorbidities, obstetric outcomes and vascular complications stratified by year.

Variable	Non-ART				ART			
	2008-2010	2011-2013	2014-2016	p_{trend}-value	2008-2010	2011-2013	2014-2016	p_{trend}-value
Deliveries	99.69%	99.67%	99.54%	---	0.31%	0.33%	0.46%	---
Age (years), median (IQR)	27 (22-32)	28 (23-32)	28 (24-32)	**<0.0001**	35 (32-39)	35 (32-39)	35 (32-39)	**0.010**
Race and ethnicity:				**<0.0001**				0.315
White	44.35%	49.28%	49.98%		66.05%	67.18%	65.41%	
Black	11.94%	13.60%	14.00%		6.59%	5.49%	5.50%	
Hispanic	18.99%	19.69%	19.18%		5.28%	5.58%	6.77%	
Asian / Pacific Islander	4.12%	4.63%	5.27%		10.16%	10.50%	11.25%	
Native American	0.78%	0.76%	0.70%		0.47%	0.55%	0.31%	
Other	4.12%	4.61%	4.40%		4.49%	5.68%	4.64%	
Missing	15.70%	7.43%	6.47%		6.95%	5.02%	6.12%	
Median ZIP code income (quartile):				**<0.0001**				**<0.0001**
1st (lowest)	26.78%	27.68%	28.66%		7.09%	6.06%	7.96%	
2nd	25.42%	24.51%	24.83%		11.67%	11.87%	13.91%	
3rd	23.74%	25.02%	24.11%		22.59%	25.66%	24.26%	
4th (highest)	21.99%	21.15%	21.10%		57.90%	55.43%	52.97%	
Missing	2.07%	1.64%	1.30%		0.75%	0.98%	0.90%	
Weekday admission	80.95%	80.71%	80.34%	**<0.0001**	82.61%	83.13%	82.92%	0.830
Length of stay (days), median (IQR)	2 (2-3)	2 (2-3)	2 (2-3)	**<0.0001**	3 (2-4)	3 (2-4)	3 (2-4)	**<0.0001**
Total charge ($), median (IQR)	10,001 (6,785-15,084)	12,077 (8,088-18,273)	14,350 (9,598-21,618)	**<0.0001**	14,092 (8,770-24,080)	18,302 (11,143-28,900)	20,432 (12,946-32,264)	**<0.0001**
Expected primary payer:				**<0.0001**				**0.008**
Medicare	0.65%	0.76%	0.75%		0.06%	0.09%	0.24%	
Medicaid	44.01%	44.72%	43.86%		3.36%	3.59%	5.24%	

Private insurance	48.85%	48.81%	49.85%		93.31%	93.20%	90.43%	
Self-pay	3.54%	2.50%	2.55%		1.50%	1.31%	1.73%	
No charge	0.25%	0.11%	0.07%		0%	0.04%	0.01%	
Other	2.70%	3.10%	2.92%		1.77%	1.77%	2.35%	
Comorbidities								
Chronic kidney disease	0.04%	0.05%	0.08%	**<0.0001**	0%	0.08%	0.07%	0.284
Congenital heart disease	0.09%	0.12%	0.16%	**<0.0001**	0.17%	0.28%	0.35%	0.072
Congestive heart failure	0.05%	0.04%	0.05%	0.893	0.14%	0.05%	0.06%	0.185
Current preeclampsia/eclampsia	4.19%	4.44%	4.65%	**<0.0001**	9.60%	9.79%	10.95%	**0.005**
Depression	1.89%	2.18%	2.59%	**<0.0001**	2.77%	2.72%	3.04%	0.248
Diabetes mellitus	1.02%	1.11%	1.18%	**<0.0001**	1.11%	0.91%	1.35%	0.092
Dyslipidemia	0.08%	0.12%	0.17%	**<0.0001**	0.23%	0.38%	0.52%	**0.016**
Hypertension	1.95%	2.22%	2.44%	**<0.0001**	4.02%	3.40%	3.75%	0.799
Multifetal pregnancy	2.21%	1.94%	1.67%	**<0.0001**	40.10%	32.15%	22.48%	**<0.0001**
Obesity	3.45%	5.34%	7.86%	**<0.0001**	3.78%	5.15%	8.07%	**<0.0001**
Previous MI	0.01%	0.01%	0.02%	**<0.0001**	0.05%	0%	0.01%	0.125
Previous TIA / stroke	0.04%	0.06%	0.08%	**<0.0001**	0.23%	0.09%	0.11%	0.159
Smoker	6.31%	7.22%	9.56%	**<0.0001**	2.16%	2.47%	5.01%	**<0.0001**
Valvular disease	0.38%	0.25%	0.21%	**<0.0001**	1.10%	0.81%	0.60%	**0.003**
Obstetric outcomes								
Cesarean delivery	32.20%	32.28%	31.86%	**<0.0001**	56.66%	54.57%	54.52%	**0.041**
Placental abruption	1.07%	1.07%	1.08%	0.766	1.92%	2.28%	1.83%	0.437
Preterm birth	7.25%	6.36%	5.07%	**<0.0001**	21.89%	17.21%	9.79%	**<0.0001**
Vascular complications								
Acute kidney injury	0.07%	0.09%	0.10%	**<0.0001**	0.37%	0.31%	0.42%	0.436
Arrhythmia	0.62%	0.77%	0.83%	**<0.0001**	1.26%	1.39%	1.52%	0.211
Ischemic stroke	0.007%	0.007%	0.008%	0.212	0%	0.04%	0.03%	0.547
Peripartum cardiomyopathy	0.028%	0.020%	0.015%	**<0.0001**	0.025%	0.025%	0.029%	0.962

Venous thromboembolism	0.04%	0.05%	0.06%	**<0.0001**	0.05%	0.11%	0.15%	0.129

ART, assisted reproductive technology. IQR, interquartile range. MI, myocardial infarction. TIA, transient ischemic attack.

Table S4. Patient characteristics stratified by assisted reproductive technology and cardiovascular disease risks.

Variable	Non-ART, no CVD risk	Non-ART, CVD risk	ART, no CVD risk	ART, CVD risk
Deliveries	79.02%	20.67%	0.17%	0.14%
Number of deliveries, weighted	27,082,915	7,084,331	58,265	47,983
Age (years), median (IQR)	28 (23-32)	28 (23-32)	35 (32-39)	35 (32-39)
Race and ethnicity:				
White	46.34%	53.43%	66.02%	66.27%
Black	12.32%	16.38%	5.13%	6.37%
Hispanic	20.78%	13.56%	5.96%	6.32%
Asian / Pacific Islander	5.31%	2.22%	11.92%	9.40%
Native American	0.70%	0.93%	0.42%	0.41%
Other	4.68%	3.19%	4.79%	5.22%
Missing	9.85%	10.29%	5.76%	6.01%
Median ZIP code income (quartile):				
1st (lowest)	26.57%	31.95%	6.92%	7.45%
2nd	24.48%	26.64%	12.04%	13.86%

3rd	24.52%	23.37%	23.91%	25.19%
4th (highest)	22.73%	16.45%	56.19%	52.64%
Missing	1.70%	1.59%	0.94%	0.86%
Weekday admission	80.09%	82.89%	81.42%	84.89%
Length of stay (days), median (IQR)	2 (2-3)	3 (2-4)	3 (2-4)	4 (3-5)
Total charge ($), median (IQR)	11,519 (7,693-17,458)	14,062 (9,137-22,026)	16,439 (10,198-25,804)	22,345 (13,769-36,206)
Expected primary payer:				
Medicare	0.54%	1.38%	0.17%	0.15%
Medicaid	42.20%	51.75%	4.06%	4.74%
Private insurance	51.06%	41.94%	92.15%	91.50%
Self-pay	3.08%	2.07%	1.57%	1.51%
No charge	0.15%	0.12%	0.03%	0.01%
Other	2.97%	2.74%	2.02%	2.09%

ART, assisted reproductive technology. CVD, cardiovascular disease. IQR, interquartile range. MI, myocardial infarction. TIA, transient ischemic attack.

Table S5. In-hospital obstetric outcomes and vascular complications (per 10,000 deliveries), stratified by assisted reproductive technology and cardiovascular disease risks.

Variable	Non-ART, no CVD risk	Non-ART, CVD risk	ART, no CVD risk	ART, CVD risk
	n=27,082,915	*n*=7,084,331	*n*=58,265	*n*=47,983
Obstetric outcomes				
Cesarean delivery	2901	4392	4472	6783
Placental abruption	91	170	186	218
Preterm birth	484	1157	612	2479
Vascular complications				
Acute kidney injury	3	31	13	69
Arrhythmia	58	133	118	174
Ischemic stroke	0.4	2.2	1.7	4.2
Peripartum cardiomyopathy	0.6	8	1.6	4.1
Venous thromboembolism	4	10	8	17

ART, assisted reproductive technology. CVD, cardiovascular disease.

Table S6. Association between pregnancies conceived by assisted reproductive techniques and in-hospital obstetric outcomes and vascular complications, stratified by cardiovascular disease risks.

	Non-ART, CVD risk	ART, no CVD risk	ART, CVD risk
OBSTETRIC OUTCOMES			
Caesarean delivery			
Unadjusted*	1.92 (1.90, 1.93)	1.98 (1.90, 2.06)	5.16 (4.88, 5.45)
Adjusted+	1.93 (1.92, 1.95)	1.48 (1.42, 1.54)	3.86 (3.65, 4.09)
Placental abruption			
Unadjusted	1.89 (1.85, 1.92)	2.07 (1.78, 2.40)	2.43 (2.13, 2.78)
Adjusted	1.81 (1.78, 1.85)	2.13 (1.83, 2.46)	2.52 (2.20, 2.88)
Preterm birth			
Unadjusted	2.57 (2.52, 2.62)	1.28 (1.18, 1.39)	6.48 (6.07, 6.92)
Adjusted	2.65 (2.60, 2.71)	1.59 (1.47, 1.71)	7.92 (7.50, 8.37)
VASCULAR COMPLICATIONS			
Acute kidney injury			
Unadjusted	10.57 (9.96, 11.22)	4.56 (2.80, 7.44)	23.95 (18.58, 30.88)
Adjusted	10.15 (9.53, 10.81)	3.97 (2.44, 6.45)	21.20 (16.41, 27.38)
Arrythmia			
Unadjusted	2.29 (2.23, 2.34)	2.04 (1.71, 2.43)	3.02 (2.55, 3.57)
Adjusted	2.25 (2.20, 2.30)	2.19 (1.84, 2.61)	3.28 (2.78, 3.87)
Ischemic stroke			
Unadjusted	5.75 (4.81, 6.86)	4.35 (1.08, 17.56)	11.03 (4.13, 29.46)
Adjusted	5.69 (4.74, 6.82)	3.05 (0.75, 12.38)	7.84 (2.94, 20.90)
Peripartum cardiomyopathy			
Unadjusted	13.23 (11.62, 15.05)	2.59 (0.65, 10.28)	6.83 (2.54, 18.39)
Adjusted	13.01 (11.36, 14.91)	2.70 (0.68, 10.72)	6.79 (2.52, 18.27)
Venous thromboembolism			
Unadjusted	2.63 (2.46, 2.81)	2.16 (1.16, 4.03)	4.32 (2.66, 7.01)
Adjusted	2.33	1.52	3.04

	(2.17, 2.50)	(0.81, 2.83)	(1.87, 4.93)

[*]Data expressed as odds ratios and 95% confidence intervals, reference group is no assisted reproductive technology and no cardiovascular disease risks.

[+]Adjustment includes age, median ZIP code income quartile, primary payer, race / ethnicity, weekend admission, and year of admission.

Table S7. In-hospital obstetric outcomes and vascular complications (per 10,000 deliveries), stratified by singleton and multifetal pregnancies.

Variable	Non-ART, singleton *n*=33,506,235	ART, singleton *n*=76,179	p-value	Non-ART, multifetal *n*=664,133	ART, multifetal *n*=30,670	p-value
Obstetric outcomes						
Cesarean delivery	3145	4722	**<0.0001**	6560	7392	**<0.0001**
Placental abruption	105	191	**<0.0001**	198	222	0.20
Preterm birth	569	711	**<0.0001**	3389	3227	**0.02**
Vascular complications						
Acute kidney injury	8	27	**<0.0001**	25	65	**<0.0001**
Arrhythmia	73	133	**<0.0001**	137	168	**0.04**
Ischemic stroke	1	3	**0.008**	1	3	0.16
Peripartum cardiomyopathy	2	2	0.89	7	5	0.51
Venous thromboembolism	5	11	**0.003**	8	17	0.23

ART, assisted reproductive technology.

Table S8. Association between pregnancies conceived by assisted reproductive techniques and in-hospital obstetric outcomes and vascular complications, stratified by singleton and multifetal pregnancies.

Variable	Singleton*		Multifetal+	
	Unadjusted‡	Adjusted§	Unadjusted	Adjusted
Obstetric outcomes				
Cesarean delivery	1.95 (1.88, 2.02)	1.44 (1.39, 1.50)	1.49 (1.36, 1.62)	1.12 (1.03, 1.21)
Placental abruption	1.83 (1.61, 2.08)	1.86 (1.64, 2.12)	1.12 (0.94, 1.34)	1.16 (0.96, 1.39)
Preterm birth	1.27 (1.18, 1.37)	1.57 (1.47, 1.68)	0.93 (0.87, 0.99)	1.10 (1.03, 1.17)
Vascular complications				
Acute kidney injury	3.24 (2.38, 4.40)	2.82 (2.06, 3.87)	2.56 (1.84, 3.57)	1.49 (1.05, 2.12)
Arrhythmia	1.84 (1.59, 2.13)	1.89 (1.63, 2.19)	1.23 (1.01, 1.51)	1.32 (1.08, 1.62)
Ischemic stroke	3.48 (1.30, 9.33)	2.13 (0.78, 5.79)	2.75 (0.63, 12.10)	3.03 (0.66, 13.82)
Peripartum cardiomyopathy	0.92 (0.30, 2.84)	1.09 (0.29, 4.04)	0.68 (0.22, 2.16)	0.54 (0.12, 2.44)
Venous thromboembolism	2.07 (1.27, 3.39)	1.43 (0.87, 2.34)	1.47 (0.78, 2.76)	1.38 (0.72, 2.66)

*Reference group is singleton pregnancy with no assisted reproductive technology.

+Reference group is multifetal pregnancy with no assisted reproductive technology.

‡Data expressed as odds ratios and 95% confidence intervals,

§Adjustment includes age, median ZIP code income quartile, primary payer, race / ethnicity, weekend admission, year of admission, chronic kidney disease, congenital heart disease, congestive heart failure, depression, diabetes, dyslipidemia, hypertension, multifetal pregnancy, obesity, preeclampsia/eclampsia, previous myocardial infarction, previous transient ischemic attack / stroke, smoker, valvular disease.

Table S9. Association between pregnancies conceived by assisted reproductive techniques and in-hospital obstetric outcomes and vascular complications within propensity score matched cohorts.

Variable	Unadjusted*	p-value	Adjusted+	p-value
Obstetric outcomes				
Cesarean delivery	2.49 (2.41, 2.57)	**<0.0001**	1.38 (1.33, 1.43)	**<0.0001**
Placental abruption	1.92 (1.73, 2.13)	**<0.0001**	1.55 (1.40, 1.72)	**<0.0001**
Preterm birth	2.64 (2.49, 2.80)	**<0.0001**	1.23 (1.17, 1.29)	**<0.0001**
Vascular complications				
Acute kidney injury	5.65 (4.53, 7.06)	**<0.0001**	2.22 (1.74, 2.83)	**<0.0001**
Arrhythmia	2.14 (1.89, 2.42)	**<0.0001**	1.57 (1.38, 1.77)	**<0.0001**
Ischemic stroke	4.47 (2.00, 10.00)	**<0.0001**	1.43 (0.54, 3.80)	0.47
Peripartum cardiomyopathy	2.43 (1.09, 5.40)	**0.03**	0.65 (0.19, 2.22)	0.49
Venous thromboembolism	2.45 (1.67, 3.58)	**<0.0001**	1.30 (0.88, 1.91)	0.19

*Data expressed as odds ratios and 95% confidence intervals, reference group is no assisted reproductive technology.

+Adjustment includes age, median ZIP code income quartile, primary payer, race / ethnicity, weekend admission, year of admission, chronic kidney disease, congenital heart disease, congestive heart failure, depression, diabetes, dyslipidemia, hypertension, multifetal pregnancy, obesity, preeclampsia/eclampsia, previous myocardial infarction, previous transient ischemic attack / stroke, smoker, valvular disease.

Table S10. Association between pregnancies conceived by assisted reproductive techniques and in-hospital obstetric outcomes and vascular complications within propensity score matched cohorts, stratified by cardiovascular disease risks.

	Non-ART, CVD risk	ART, no CVD risk	ART, CVD risk
OBSTETRIC OUTCOMES			
Caesarean delivery			
Unadjusted*	2.01 (1.99, 2.02)	1.89 (1.81, 1.96)	4.92 (4.65, 5.19)
Adjusted+	1.98 (1.96, 1.99)	1.49 (1.43, 1.55)	3.89 (3.68, 4.12)
Placental abruption			
Unadjusted	1.94 (1.90, 1.98)	2.07 (1.78, 2.40)	2.44 (2.13, 2.79)
Adjusted	1.87 (1.83, 1.91)	2.13 (1.84, 2.48)	2.53 (2.21, 2.89)
Preterm birth			
Unadjusted	2.80 (2.75, 2.86)	1.33 (1.23, 1.44)	6.72 (6.30, 7.17)
Adjusted	2.96 (2.90, 3.02)	1.63 (1.52, 1.76)	8.17 (7.73, 8.64)
VASCULAR COMPLICATIONS			
Acute kidney injury			
Unadjusted	8.75 (8.19, 9.35)	4.62 (2.83, 7.54)	24.27 (18.80, 31.32)
Adjusted	8.55 (7.96, 9.19)	3.92 (2.41, 6.38)	21.01 (16.22, 27.21)
Arrythmia			
Unadjusted	2.13 (2.08, 2.19)	2.11 (1.77, 2.52)	3.13 (2.64, 3.70)
Adjusted	2.11 (2.06, 2.17)	2.17 (1.82, 2.58)	3.23 (2.74, 3.82)
Ischemic stroke			
Unadjusted	4.63 (3.77, 5.68)	4.35 (1.08, 17.57)	11.02 (4.13, 29.42)
Adjusted	4.48 (3.63, 5.54)	3.22 (0.79, 13.13)	8.14 (3.04, 21.77)
Peripartum cardiomyopathy			
Unadjusted	5.68 (4.87, 6.63)	2.56 (0.64, 10.17)	6.76 (2.51, 18.19)
Adjusted	5.32 (4.54, 6.24)	2.55 (0.65, 10.10)	6.42 (2.37, 17.37)
Venous thromboembolism			
Unadjusted	2.28 (2.11, 2.47)	2.08 (1.12, 3.88)	4.16 (2.56, 6.75)

Adjusted	1.98 (1.82, 2.15)	1.45 (0.78, 2.71)	2.90 (1.79, 4.72)

*Data expressed as odds ratios and 95% confidence intervals, reference group is no assisted reproductive technology and no cardiovascular disease risks.

+Adjustment includes age, median ZIP code income quartile, primary payer, race / ethnicity, weekend admission, and year of admission.

Table S11. Balancing of variables in the propensity matched cohorts.

Variable	Mean		% bias	t-test	p-value
	ART	Non-ART			
Race	2.12	2.12	0.1	0.08	0.94
Age	35.60	35.60	0.0	0.01	0.99
Congenital heart disease	0.0030	0.0029	0.2	0.18	0.86
Smoker	0.0363	0.0362	0.1	0.08	0.94
Previous myocardial infarction	0.0001	0.0001	0.0	-0.00	1.000
Previous stroke	0.0012	0.0011	0.3	0.28	0.78
Dyslipidaemia	0.0042	0.0040	0.4	0.38	0.71
Valvular disease	0.0076	0.0074	0.3	0.22	0.83
Depression	0.0287	0.0290	-0.2	-0.17	0.86
Diabetes mellitus	0.0116	0.0115	0.1	0.13	0.89
Renal failure	0.0006	0.0006	0.1	0.13	0.89
Obesity	0.0633	0.0635	-0.1	-0.08	0.94
Chronic heart failure	0.0007	0.0006	0.4	0.38	0.71

Ps R2	LR chi2	p>chi2	Mean bias	Median bias	B	R	% variation
0.000	0.53	1.00	0.2	0.2	0.7	1.11	0

Figure S1. Temporal trend in prevalence of pregnancies conceived by assisted reproductive techniques between 2008 and 2016.