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INCREASED RISK OF SEVERE MATERNAL MORBIDITY AMONG INFERTILE WOMEN: ANALYSIS OF US CLAIMS DATA

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Abstract

Background: Severe maternal morbidity continues to be an issue of national and global concern and is increasing in incidence. The incidence of infertility is also on the rise, and infertile women experience a higher risk of incident chronic medical disease and cancer, suggesting that fertility may serve as a window to a woman's overall health.

Objective: To investigate the risk of severe maternal morbidity by maternal fertility status.

Study Design: Retrospective cohort analysis using Optum's de-identifed Clinformatics® Data Mart Database between 2003–2015. Infertile women stratified by infertility diagnosis, testing or treatment were compared to fertile women seeking routine gynecologic care. In both groups, only women who underwent pregnancy and delivery of a singleton during the follow up period were included. Main outcomes were severe maternal morbidity indicators, defined by the CDC, and identified by ICD-10 and CPT codes within 6 weeks of each delivery. Results were adjusted for maternal age, race, education, nulliparity, race, smoking, obesity, delivery mode, preterm birth, number of prenatal visits, and year of delivery.

Results: 19,658 women comprised the infertile group and 525,695 women comprised the fertile group. The overall incidence of any severe maternal morbidity indicator was 7.0% among women receiving fertility treatment, 6.4% among women receiving a fertility diagnosis, 5.5% among women receiving fertility testing and 4.3% among fertile women.. Overall, infertile women had a significantly higher risk of developing any severe maternal morbidity indicator (AOR 1.22, CI 1.14–1.31, p<0.01) as well as a significantly higher risk of disseminated intravascular coagulation

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(DIC) (AOR 1.48, CI 1.26 – 1.73, p<0.01), eclampsia (AOR 1.37, CI 1.05 – 1.79, p<0.01), heart failure during procedure or surgery (AOR 1.54, CI 1.21 – 1.97, p<0.01), internal injuries of the thorax, abdomen or pelvis (AOR 1.59, CI 1.12 – 2.26, p<0.01), intracranial injuries (AOR 1.77, CI 1.20– 2.61, p<0.01), pulmonary edema (AOR 2.18, CI 1.54 – 3.10, p<0.01), thrombotic embolism (AOR 1.58, CI 1.14 – 2.17, p<0.01), and blood transfusion (AOR 1.50, CI 1.30 – 1.72, p<0.01) compared to fertile women. Fertile women did not face a significantly higher risk of any maternal morbidity indicator compared to infertile women. In a subgroup analysis by maternal race/ethnicity, compared to Caucasian women, the risks of severe maternal morbidity were significantly higher for fertile Black women compared to fertile Caucasian women, while risks were similar between infertile Black women and infertile Caucasian women.

Conclusion: Using an insurance claims database, we report that women diagnosed with infertility and women receiving fertility treatment experience a significantly higher risk of multiple indicators of severe maternal morbidity compared to fertile women. The increased risk of severe maternal morbidity noted among fertile Black women compared to fertile Caucasian women is attenuated among infertile Black women, who face similar risks as infertile Caucasian women.

Condensation:

Infertile women face a significantly higher risk of multiple indicators of severe maternal morbidity compared to fertile women based on insurance claims data.

Keywords

female infertility; fertility treatment; severe maternal morbidity; maternal mortality; racial disparities

Introduction

Severe maternal morbidity continues to be an issue of national and global concern and is associated with maternal mortality, increased health care costs, and significant family burden.[1] The incidence of severe maternal morbidity in the US is on the rise, from 70/1000 deliveries in 1999 to 160/10,000 deliveries in 2011.[2] Severe maternal morbidity has been defined by the CDC to include any of twenty five indicators present during the delivery admission[3] and attributed to a variety of medical and socioeconomic factors.[4]

The incidence of infertility and utilization of assisted reproductive technology (ART) are on the rise, and infertile women experience a higher risk of incident chronic medical disease[5] and cancer,[6] suggesting that fertility may serve as a window to a woman's overall health. It has also been consistently reported that infertile women are at higher risk for adverse pregnancy outcomes and morbid perinatal events.[1,7,8,9] The risks faced by infertile women have been stratified by age,[1] fertility status (subfertile versus in vitro fertilization treatment),[7] oocyte source (autologous versus donor),[8] and embryo state (fresh versus thawed).[8] The profile of the patient population receiving assisted reproductive technology (ART), however, tends to reflect greater social advantage and factors traditionally protective against severe maternal morbidity compared to the general maternity population.[10]

Race has been consistently associated with maternal morbidity and mortality, with Black women facing a several-fold higher risk of morbidity and mortality than any other race or ethnicity (11, 12). While race might serve as a marker for sociodemographic risk factors, the etiology of the racial disparity in pregnancy-related morbidity and mortality is unclear (13,14). We sought to first characterize the risk of severe maternal morbidity among infertile women compared to fertile women and stratify this risk by maternal race to further understand the complex interaction between race, infertility and maternal health risk.

Materials and Methods

Patients

We analyzed subjects in Optum's de-identifed Clinformatics® Data Mart Database between 2003–2015. Optum©'s de-identifed Clinformatics® Data Mart Database (CDM) is derived from a database of administrative health claims for members of a large, national managed care company affiliated with Optum. The database includes approximately 17–19 million annual covered lives, for a total of over 57 million unique lives over an 11 year period (1/2005 through 12/2016). These administrative claims submitted for payment by providers and pharmacies are verified, adjudicated, adjusted, and de-identified prior to inclusion. The Clinformatics® Data Mart data comprises both commercial and Medicare Advantage health plan data. The population is geographically diverse, spanning all 50 states. This study was exempt from review by the Stanford Institutional Review Board because it contained secondary use, de-identified data.

Characterization of the infertile and fertile groups is described in detail previously by our group.[5,6] In brief, the group of infertile women was comprised of women receiving any of the following: 1) an infertility diagnosis, 2) fertility testing, or 3) fertility treatment who become pregnant and delivered during enrollment. Women with an infertility diagnosis were identified by outpatient claims. Fertility testing was identified through diagnosis codes or the presence of a procedure code (CPT) for hysterosalpingogram (HSG). Patients receiving fertility treatment were identified by the presence of a CPT code for intra-uterine artificial insemination, follicular puncture for oocyte retrieval, or intrauterine embryo transfer. The presence of a pharmacy claim for a prescription for clomiphene citrate or a gonadotropin (Follicle Stimulating Hormone, FSH, Human Menopausal Gonadotropin, HMG, Human Chorionic Gonadotropin, HCG) was also used to identify patients receiving fertility treatment.

The comparison group was composed of women receiving routine gynecologic care who did not have an infertility diagnosis or any procedure codes for fertility testing or treatment, and also become pregnant and delivered during enrollment. These patients were identified through: 1) the presence of a claim for a well woman visit, or an encounter for 2) contraceptive management, 3) placement or removal of an IUD, 4) placement of a contraceptive implant, 5) encounter for contraceptive surveillance, or 6) pap smear.

We recorded the first date of a relevant diagnosis or procedure code as the index date. For patients in the infertile group, the index date was the date of infertility diagnosis, testing or treatment. For patients in the fertile group, the index date was the date of encounter for any

of the services listed above. In order to be included in the study, patients were required to be enrolled in a plan covered by the database for at least 6 months before and after the index date, to be between 20 and 45 years old on the index date, and to become pregnant and have a delivery during enrollment and after the index date. Pregnancy and delivery were identified by diagnosis and procedure codes indicating the end of a pregnancy and are listed in a prior publication.[6] One woman was allowed to contribute multiple deliveries. Only singleton deliveries were included in the analysis using diagnosis codes provided in Supplementary Table 1. In all groups, patients with a prior cancer diagnosis or with a cancer diagnosis within the six months following the index date were excluded from the study as described in a prior publication.[6] In addition, women with twin or higher order multiple deliveries were excluded from both groups using diagnosis codes provided in Supplementary Table 1b. Finally, women who had a diagnosis of any of the twenty-five maternal morbidity indicators defined by the CDC prior to the index date were excluded from both groups. For example, a woman with a prior history of acute MI was not included in either group to limit potential confounding.

Outcome Ascertainment

Severe maternal morbidity has been defined by the CDC to include any of twenty five indicators present during the delivery through six weeks postpartum (3) and were the outcomes of this study. Severe maternal morbidity indicators were identified using diagnosis codes (Supplementary Table 2) occurring within 6 months of the delivery. Intracranial injuries include conditions causing hemiparesis or focal neurologic deficits and include intracranial hemorrhage. Outcomes with less than 11 absolute number of events were required to be reported as < 11 to protect patient privacy per the data usage agreement with Optum.

Confounder Selection

Risk of severe maternal morbidity has been attributed to a range of demographic factors including extremes of maternal age, poor reproductive history, limited access to care, non-white race, smoking and obesity and low level of education.[1–4] In CDM, several demographic factors are available including maternal age, year of delivery, race and highest level of education. For each patient, diagnosis codes were then used to identify obesity (278.0, E66.9, E66.01, E66.3, E66.2), smoking (305.1, V15.82, F17.200, Z87.891), hypertension (I10, 401–405), nulliparity (V22.0, V23.81, V23.83, O0.95, O0.96), delivery mode (Supplementary Tables 3a, 3b), and preterm birth (Supplementary Table 4). Diagnosis codes entered either at the index date or during the follow up period were included. As a proxy measure of access to care, for each patient, the number of outpatient visits 280 days before each delivery was recorded.

Statistical Analysis

The risk of severe maternal morbidity by fertility status was assessed using a generalized estimating equation (GEE) model, adjusted for maternal age at index date, year of delivery, nulliparity, race, smoking, obesity, delivery mode, preterm birth, number of prenatal visits, and level of education, accounting for those who had more than one delivery during the

enrollment period. All p values were 2-sided with $p<0.05$ considered statistically significant. Analyses were performed using SAS (version 9.4, SAS Institute, Inc., Cary, NC, USA).

Subgroup Analysis by Race/Ethnicity

To evaluate the incidence of severe maternal morbidity by maternal race, a subgroup analysis was performed. Among patients with any indicator of severe maternal morbidity, risks were compared within infertile and fertile subgroups by Asian, Hispanic and Black race, with Caucasian women as the reference group.

Results

Patient Demographics: Infertile vs Fertile Patients

Of 19,658 infertile patients, 36% (n=7,113) underwent fertility treatment, 58% (n=11,548) received an infertility diagnosis, and 5% (n=997) underwent fertility testing. v525,695 patients comprised the fertile comparison group. Patients in the infertile group were older at the time of delivery (33.9±4.8 years) than their fertile counterparts (31.3±4.9 years), were followed for 3.0±3.0 years (compared to 2.9±2.9 years in the fertile group), and were more likely to be nulliparous, obese, and hypertensive, and less likely to be smokers. Women in the infertile group were more likely to deliver via cesarean section and have a preterm delivery. In both groups, the majority of patients were Caucasian (64.9% and 65.9%); 6.7% of the infertile group and 9% of the fertile group were Black; 9.5% of the infertile group and 12.7% of the fertile group were Hispanic. Education level, income and geographic distribution were similar between the infertile and fertile groups. Demographics of infertile patients further subdivided into treatment, diagnosis and testing groups are shown in Table 1. 16% of infertile women and 14% of fertile women contributed more than one pregnancy. In the GEE model, repeated measures were used to account for cases when women contributed more than one pregnancy

Comparison of Maternal Morbidity Indicators between Infertile and Fertile Groups

The incidence of severe maternal morbidity by fertility group is shown in Table 2a. The overall incidence of any severe maternal morbidity indicator was 7.0% among women receiving fertility treatment, 6.4% among women receiving a fertility diagnosis, 5.5% among women receiving fertility testing and 4.3% among fertile women. Overall, infertile women had a significantly higher risk of developing any severe maternal morbidity indicator (AOR 1.22, CI 1.14–1.31, $p<0.01$) as well as significantly higher risk of DIC (AOR 1.48, CI 1.26 – 1.73, $p<0.01$), eclampsia (AOR 1.37, CI 1.05 – 1.79, $p<0.01$), heart failure during procedure or surgery (AOR 1.54, CI 1.21 – 1.97, $p<0.01$), internal injuries of the thorax, abdomen or pelvis (AOR 1.59, CI 1.12 – 2.26, $p<0.01$), intracranial injuries (AOR 1.77, CI 1.20– 2.61, $p<0.01$), pulmonary edema (AOR 2.18, CI 1.54 – 3.10, $p<0.01$), thrombotic embolism (AOR 1.58, CI 1.14 – 2.17, $p<0.01$), and blood transfusion (AOR 1.50, CI 1.30 – 1.72, $p<0.01$) compared to fertile women (Table 2b). Infertility treatment is additionally associated with increased risk of acute respiratory distress (AOR 1.57, CI 1.03–2.38), shock (AOR 1.76, CI 1.02–3.05), and hysterectomy (AOR 1.61, CI 1.03–2.52) compared to fertile women. Infertility diagnosis is additionally associated with increased risk of cardiac arrest or ventricular fibrillation (AOR 2.68, CI 1.16–6.20), intracranial injuries (AOR 2.64, CI 1.14–

6.10), puerperal cardiovascular disorders (AOR 1.41, CI 1.13–1.75), and cardiology monitoring (AOR 1.14, CI 1.02–1.27) compared to fertile women. Women undergoing fertility testing without a diagnosis of infertility or fertility treatment did not have an increased risk of any maternal morbidity indicator. Due to the low number of events for aneurysm, sickle cell anemia with crisis and temporary tracheostomy, adjusted odds ratios were not able to be computed. The risk of acute MI, acute renal failure, acute respiratory distress, amniotic fluid embolism (AFE), cardiac arrest or ventricular fibrillation, intracranial injuries, puerperal cardiovascular disorders, severe anesthesia complications, sepsis, shock, cardiology monitoring, conversion of cardiac rhythm, hysterectomy, operations on the heart and pericardium, ventilation and intubation were similar between the overall infertile and fertile groups. Fertile women did not face a significantly higher risk of any severe maternal morbidity indicator compared to infertile women.

Subgroup Analysis by Race/Ethnicity

The risk of developing any maternal morbidity indicator stratified by maternal race is shown in Table 3. Compared to fertile Caucasian women, fertile Black women had significantly higher risk of any severe maternal morbidity indicator (AOR 1.34, CI 1.28–1.40). Among infertile Black women, however, this trend is not significant after adjustment for covariates among Black women receiving fertility treatment compared to Caucasian women (AOR 1.20, CI 0.80–1.81) or among Black women diagnosed with infertility compared to Caucasian women (AOR 1.30, CI 0.99–1.70). Asian and Hispanic women in both fertile and infertile subgroups had similar adjusted risks of severe maternal morbidity compared to Caucasian women.

Comment

Principal Findings of the Study—The overall incidence of any severe maternal morbidity indicator was significantly higher among infertile women receiving fertility treatment (7.0%) and women diagnosed with infertility (6.4%) compared to fertile women (4.3%) with private insurance. Specifically, infertile women receiving fertility treatment have significantly higher risks of eight of the twenty-five severe maternal morbidity indicators tracked by the CDC, including over 50% increased risk of respiratory distress, DIC, pulmonary edema, shock, blood transfusion and hysterectomy and, 50% increased risk of eclampsia. Woman diagnosed with infertility had over 2-fold increased risk of cardiac arrest, intracranial injury, and pulmonary edema, and over 50% increased risk of intra-operative heart failure and thrombotic embolism. Women undergoing fertility testing without a diagnosis of infertility or fertility treatment did not have an increased risk of any maternal morbidity indicator, although these results are limited by the small size of the subgroup (5% of the overall infertile cohort). These morbidity indicators, however rare, result in significant financial and family burden, and are strongly associated with an increased subsequent risk of maternal mortality, which is a truly catastrophic event.[1]

Results and Clinical Implications

Literature examining the association between infertility and maternal morbidity indicators has not previously examined the role of race. In the general obstetric population, Black

women have a substantially higher risk of morbidity and mortality than any other race or ethnicity.[12,13] This association is likely multifactorial and may be due in part to differences in socioeconomic status.[13,14] Women who utilize infertility services are more likely to be non-Hispanic white, and more highly educated and affluent than fertile women.[13–23] We sought to determine if racial disparities in severe maternal morbidity indicators persist even among infertile women. Our findings among fertile women are consistent with prior reports, with fertile Black women facing a significant higher risk of severe maternal morbidity compared to fertile Caucasian women. Among infertile Black women, however, this trend is attenuated. Before adjusting for covariates including maternal age, year of delivery, nulliparity, education, delivery mode, preterm birth, obesity, smoking, hypertension, diabetes, and number of prenatal visits, risk of severe maternal morbidity was higher among black women with either an infertility diagnosis or undergoing fertility treatment compared to their Caucasian counterparts. After adjustment for covariates, we report that infertile black women face similar risks as infertile Caucasian women, suggesting that additional confounding factors including socioeconomic status may play a larger role in these observed differences. Prior reports indicate a higher risk of severe maternal morbidity among Asian and Hispanic subpopulations[24,25] but these studies have not been undertaken in an infertile patient population. We found that Asian and Hispanic women in both fertile and infertile subgroups had similar adjusted risks of severe maternal morbidity compared to Caucasian women. Understanding ethnicity-based differences in obstetric outcomes is the first step towards improving care for pregnant women.

Research Implications

The overall incidence of severe maternal morbidity that we report is higher than prior reports of severe maternal morbidity in both fertile and infertile patient populations and can be attributed to multiple factors. This study utilized the original list of 25 SMM indicators based on the 9th Revision of ICD that was published in 2012; estimates of overall maternal morbidity may be higher due to including a higher number of indicators. In addition, prior studies have either looked at different patient populations or obtained information from different sources all of which may contribute to the differences observed. For example, Callaghan et al utilized a hospital inpatient care database to report the incidence of all twenty-five severe maternal morbidity indicators among a national sample of community hospitals.[3] The incidence of the same morbidity indicators among the infertile population we analyzed is approximately 10-fold higher than the overall US population.[1–3,11] The increased risk of severe maternal morbidity among infertile women has been acknowledged in prior publications, although a comprehensive comparison of all twenty-five severe maternal morbidity indicators tracked by the CDC between infertile and fertile patient population has not been performed and existing studies may have limitations. Luke et al compared the incidence of any severe maternal morbidity event among 1,477,522 pregnancies subdivided into fertile, subfertile and IVF patient populations using data from the Society for Assisted Reproductive Technology (SART) linked to birth certificates[8].

Among singleton deliveries, the incidence of any severe maternal morbidity was 0.01% among fertile women and 0.02% among subfertile women and infertile women undergoing IVF. Despite similar patient populations, the difference in the incidence of severe maternal

morbidity between the results by Luke et al and our findings may be due to substantial under-reporting of severe maternal morbidity on the birth certificate, as well as the more limited number of indicators (six items on the birth certificate versus 25 items in our analysis).[26–8] Claims-based data also has limitations which will be discussed below, and highlights the need for additional study of this important clinical question.

Study Strengths and Limitations

Strengths of this study include the large dataset utilized, controlling for multiple confounders, stratifying outcomes by infertility treatment, diagnosis and testing, maternal race, and restricting the analysis to singleton deliveries. The exclusion of twin and higher order multiple deliveries would lead us to tend to underestimate the infertility associated complications. Despite this, we found a significantly higher risk of severe maternal morbidity among infertile versus fertile women.

While the number of patients was large, the main limitation of this study is the low incidence of severe maternal morbidity. In particular, the results of the subgroup analysis by maternal race are limited by the low number of individual severe maternal morbidity indicators. However, we found an approximately 10-fold higher incidence of severe maternal morbidity indicators compared to similar studies using inpatient hospital claims data.[3] Furthermore, population health-level databases are subject to a variety of limitations, which we have detailed in a prior publication.[6] In brief, there is selection bias of the study population as a whole because only insured patients are included, and these results may not be generalizable to women with public insurance. In addition, in the absence of linkage to a population-based registry, we are unable to distinguish subject misidentification or loss of continuity. There may be a bias within the infertility population and coding, which may be affected by states with and without insurance mandates, resulting in out of pocket infertility treatments that may not be accounted for. We expect, however, that this misclassification would be non-differential, which would shift the results towards the null so any association we identify is likely to be underestimated. Finally, due to the high number of outcomes investigated, there is a possibility that a small fraction of the results are false positives due to the role of chance. 31% of the associations we investigated were statistically significant. Chance alone may account for, on average, one false positive but would be unlikely to explain all of them. Given the exploratory nature of the results and the rarity of the outcomes, we await confirmation of our findings from future studies. We also hope to explore associations between severe maternal morbidity and etiologies of infertility and types of fertility treatment in future studies to better understand the relationship between infertility and maternal morbidity. In addition, future studies should incorporate additional covariates pertaining to pregnancy including conditions of abnormal placentation or pre-eclamspsia.

Conclusions

Women diagnosed with infertility and women receiving fertility treatment experience a significantly higher risk of multiple indicators of severe maternal morbidity compared to fertile women. In a subgroup analysis by maternal race/ethnicity, compared to Caucasian women, the risks of severe maternal morbidity were significantly higher for fertile Black

women compared to fertile Caucasian women, while this trend is attenuated among infertile Black women, who face similar risks as infertile Caucasian women.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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AJOG at a Glance:

A. The objective of this study was to investigate the risk of severe maternal morbidity by maternal fertility status.

B. Using an insurance claims database, we report that women diagnosed with infertility and women receiving fertility treatment face a significantly higher overall risk of any severe maternal morbidity indicator compared to fertile women. Specifically, infertile women have significantly higher risks of eight of the twenty-five severe maternal morbidity indicators tracked by the CDC. In a subgroup analysis by maternal race/ethnicity, compared to Caucasian women, the risks of severe maternal morbidity were significantly higher for fertile Black women compared to fertile Caucasian women, while this trend is attenuated among infertile Black women, who face similar risks as infertile Caucasian women.

C. In a privately insured population, women diagnosed with infertility and women receiving fertility treatment experience a significantly higher risk of multiple indicators of severe maternal morbidity compared to fertile women.

Table 1.

Demographic Characteristics of the Infertile and Fertile Groups

		Infertile			Fertile
		Treatment	**Diagnosis**	**Testing**	
	N	7,113	11,548	997	525,695
Maternal Age At Delivery (years)	Mean (SD)	35.3 (4.5)	33.0 (4.8)	33.2 (4.6)	31.2 (4.9)
	% 20–24	0.7	3.6	3.1	8.7
	25–29	9.5	20.8	18.2	28.6
	30–34	32.8	37.5	39.8	37.9
	35–39	38.6	28.6	30.3	20.1
	40–44	16.7	8.7	8.2	4.4
	≥45	1.6	0.8	**	0.4
Follow-up (years) from delivery to last database enrollment date	Mean (SD)	3.3 (3.1)	2.9 (2.9)	2.5 (2.7)	2.9 (2.9)
	% < 1 year	30.2	33.7	40	33.9
	1–2 years	17.1	18.7	18.9	18.3
	2–3 years	11.4	11.8	10.3	12.1
	3–4 years	8.7	8.7	8	8.8
	> 4 years	32.6	27.1	22.8	26.9
Nulliparous	%	50.2	45.4	49.3	42.2
Prepregnancy	Obesity %	9.9	12.4	9.9	8.8
	Smoker %	3.9	5.7	5.4	6.1
	Diabetes %	6.1	5.9	3.7	3.3
Chronic hypertension	%	7.1	7.8	6.3	5.8
Mode of delivery	Vaginal %	51.9	57	58.1	67.0
	Cesarean %	48.1	43	41.9	33.0
Preterm birth	%	8.8	7.4	6.1	5.5
Year of delivery	2003–07 %	34.2	31.3	24.1	28.9
	2008–12 %	39.2	38	32.8	40.9
	2013–15 %	26.7	30.7	43.1	30.2
Maternal race/ethnicity	Caucasian %	65.7	64	70.5	65.9
	Asian %	15.9	12	9.8	7.8
	Black %	5.1	7.8	5	9
	Hispanic %	7.2	10.9	10.3	12.7
	Unknown %	6.1	5.3	4.3	4.7
Education	< 12^{th} grade %	0.2	0.3	**	0.7

		Infertile			Fertile
		Treatment	**Diagnosis**	**Testing**	
	High school diploma %	11.6	20.1	12.4	22.7
	< Bachelor degree %	45.6	51.6	55.3	53.9
	≥Bachelor degree %	42.1	27.4	31.5	22.3
	Unknown %	0.5	0.6	**	0.4
Income	<$50,000 %	6.4	12.3	11.1	15.1
	$50,000–100,000 %	19	24.3	26.2	25.2
	>$100,000 %	46.3	31.1	31.7	28.4
	Unknown %	28.4	32.3	31	31.4
Region of the country	Midwest %	27	26.8	28.3	27.7
	Northeast %	22.8	11.9	7.2	10
	South %	28.5	41.7	39.8	43.8
	West %	21.7	19.4	24.7	18.5
	Unknown %	**	0.2	0	0.1

Table 2a.

Incidence (%) of Severe Maternal Morbidity by Fertility Group

	Infertile			Fertile
	Treatment	**Diagnosis**	**Testing**	
N, deliveries	7,113	11,548	997	525,695
Severe maternal morbidity indicator				
Any severe maternal morbidity indicator (%)	7.00	6.40	5.48	4.31
Acute myocardial infarction	*	*	*	0.01
Acute renal failure	*	0.10	*	0.08
Acute respiratory distress	0.34	0.22	*	0.14
Amniotic fluid embolism	*	*	*	0.02
Aneurysm	*	*	*	0.01
Cardiac arrest or ventricular fibrillation	*	*	*	0.01
Disseminated intravascular coagulation	1.19	0.75	*	0.44
Eclampsia	0.41	0.36	*	0.22
Heart failure during procedure or surgery	0.35	0.40	*	0.17
Internal injuries of the thorax, abdomen, or pelvis	0.18	0.16	*	0.09
Intracranial injuries	*	*	*	0.02
Puerperal cardiovascular disorders	0.61	0.75	*	0.40
Pulmonary edema	0.21	0.22	*	0.08
Severe anesthesia complications	*	*	*	0.07
Sepsis	0.17	0.11	*	0.14
Shock	0.20	0.10	*	0.07
Sickle cell anemia with crisis	*	*	*	0.01
Thrombotic embolism	0.28	0.31	*	0.13
Blood transfusion	1.51	1.05	1.11	0.65
Cardiology monitoring	2.90	3.07	2.13	2.24
Conversion of cardiac rhythm	*	*	*	0.01
Hysterectomy	0.30	0.16	*	0.09
Operations on the heart and pericardium	0.23	0.15	*	0.10
Temporary tracheostomy	*	*	*	**
Ventilation	0.30	0.32	*	0.22
Intubation	*	*	*	0.04

*<11 cases, true value not reported per data usage agreement

Table 2b.

Risk of Severe Maternal Morbidity by Fertility Group*

	AOR (95% CI)			
	Infertile			
	Treatment vs Fertile	Diagnosis vs Fertile	Testing vs Fertile	All infertile vs fertile
Severe maternal morbidity indicator				
Any severe maternal morbidity indicator	1.24 (1.12 – 1.37)	1.22 (1.13 – 1.33)	1.09 (0.81 – 1.45)	1.22 (1.14 – 1.31)
Acute myocardial infarction	1.68 (0.52 – 5.46)	0.90 (0.22 – 3.69)	**	1.33 (0.52 – 3.36)
Acute renal failure	1.03 (0.53 – 2.02)	0.86 (0.47 – 1.57)	**	0.84 (0.51 – 1.38)
Acute respiratory distress	1.57 (1.03 – 2.38)	1.14 (0.76 – 1.71)	**	1.26 (0.93 – 1.70)
Amniotic fluid embolism	1.61 (0.50 – 5.18)	1.10 (0.35 – 3.49)	**	1.31 (0.57 – 3.02)
Aneurysm	**	**	**	**
Cardiac arrest or ventricular fibrillation	1.22 (0.29 – 5.04)	2.68 (1.16 – 6.20)	**	1.94 (0.88 – 4.31)
Disseminated intravascular coagulation	1.67 (1.33 – 2.09)	1.34 (1.08 – 1.66)	1.57 (0.81 – 3.04)	1.48 (1.26 – 1.73)
Eclampsia	1.49 (1.02 – 2.17)	1.30 (0.95 – 1.79)	0.41 (0.06 – 2.91)	1.37 (1.05 – 1.79)
Heart failure during procedure or surgery	1.27 (0.85 – 1.91)	1.75 (1.3 – 2.36)	0.89 (0.22 – 3.57)	1.54 (1.21 – 1.97)
Internal injuries of the thorax, abdomen, or pelvis	1.61 (0.92 – 2.84)	1.52 (0.95 – 2.45)	0.99 (0.14 – 7.08)	1.77 (1.20 – 2.61)
Intracranial injuries	1.27 (0.31 – 5.28)	2.64 (1.14 – 6.10)	**	2.05 (0.97 – 4.32)
Puerperal cardiovascular disorders	1.05 (0.77 – 1.43)	1.41 (1.13 – 1.75)	1.65 (0.81 – 3.35)	0.94 (0.66 – 1.33)
Pulmonary edema	1.85 (1.09 – 3.14)	2.05 (1.36 – 3.08)	**	2.18 (1.54 – 3.10)
Severe anesthesia complications	0.33 (0.08 – 1.35)	0.85 (0.42 – 1.71)	**	1.13 (0.49 – 2.60)
Sepsis	1.04 (0.58 – 1.85)	0.70 (0.40 – 1.21)	1.37 (0.34 – 5.51)	0.90 (0.59 – 1.36)
Shock	1.76 (1.02 – 3.05)	1.06 (0.58 – 1.93)	**	1.14 (0.72 – 1.80)
Sickle cell anemia with crisis	**	**	**	**
Thrombotic embolism	1.35 (0.86 – 2.13)	1.77 (1.27 – 2.49)	1.21 (0.30 – 4.88)	1.58 (1.14 – 2.17)
Blood transfusion	1.69 (1.39 – 2.07)	1.30 (1.08 – 1.56)	1.44 (0.79 – 2.62)	1.50 (1.30 – 1.72)
Cardiology monitoring	1.01 (0.87 – 1.18)	1.14 (1.02 – 1.27)	0.83 (0.53 – 1.29)	1.09 (0.997 – 1.20)
Conversion of cardiac rhythm	0.72 (0.10 – 5.29)	0.95 (0.23 – 3.88)	**	0.83 (0.26 – 2.68)
Hysterectomy	1.61 (1.03 – 2.52)	1.10 (0.69 – 1.77)	1.53 (0.38 – 6.16)	1.35 (0.97 – 1.88)
Operations on the heart and pericardium	1.44 (0.86 – 2.39)	1.09 (0.67 – 1.77)	2.23 (0.72 – 6.96)	1.12 (0.77 – 1.64)
Temporary tracheostomy	**	**	**	**
Ventilation	0.95 (0.61 – 1.47)	1.08 (0.78 – 1.51)	**	0.91 (0.69 – 1.20)
Intubation	0.92 (0.29 – 2.92)	0.98 (0.40 – 2.39)	**	0.84 (0.39 – 1.80)

*GEE (generalized estimating equation) model was used to estimate the odds ratios of the diseases between infertile and control groups, adjusted for maternal age, year of delivery, nulliparity, delivery mode, preterm birth, obesity, smoking, hypertension, diabetes, number of prenatal visits, race and ethnicity, and education, accounting for women who had more than one delivery of a singleton during the database enrollment period.

**Calculation of AOR and 95% CI not possible due to small numbers

Table 3.

Incidence (%) and Risk of Any Severe Maternal Morbidity by Maternal Fertility Status and Race/Ethnicity*

	Infertile							Fertile		
	All	Treatment		Diagnosis		Testing				
	%	Crude OR (95% CI)	AOR (95% CI)	Crude OR (95% CI)	AOR (95% CI)	Crude OR (95% CI)	AOR (95% CI)	%	Crude OR (95% CI)	AOR (95% CI)
All women	6.57							4.31		
Caucasian	6.37	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	4.09	1.00 (Reference)	1.00 (Reference)
Black	9.62	1.53 (1.04 – 2.26)	1.20 (0.80 – 1.81)	1.63 (1.27 – 2.11)	1.30 (0.99 – 1.70)	0.88 (0.20 – 3.79)	0.61 (0.13 – 2.83)	6.52	1.64 (1.57–1.71)	1.34 (1.28, 1.40)
Hispanic	7.39	1.16 (0.81 – 1.66)	1.05 (0.72 – 1.52)	1.17 (0.91 – 1.49)	0.98 (0.75 – 1.26)	1.68 (0.75 – 3.76)	1.19 (0.49 – 2.85)	4.65	1.14 (1.10–1.19)	1.04 (0.99, 1.09)
Asian	5.14	0.86 (0.65 – 1.14)	0.90 (0.67 – 1.22)	0.68 (0.51 – 0.90)	0.69 (0.51 – 0.93)	1.54 (0.66 – 3.59)	1.79 (0.73 – 4.39)	3.46	0.84 (0.79–0.89)	0.90 (0.85, 0.96)

*GEE (generalized estimating equation) model was used to estimate the odds ratios of any severe maternal morbditiy indicator between infertile and control groups, adjusting for maternal age, year of delivery, nulliparity, education, delivery mode, preterm birth, obesity, smoking, hypertension, diabetes, and number of prenatal visits, accounting for those who had more than one delivery during the database enrollment period.

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