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The Impact of Fertility Treatment on Severe Maternal Morbidity

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Abstract

Objective—To determine if fertility treatment is associated with increased risk of severe maternal morbidity (SMM) compared to spontaneous pregnancies.

Design—Retrospective cohort study

Setting—Single academic medical center

Patients—In 2012, 6543 women delivered live births >20 weeks gestation at our center. Women were categorized based on mode of conception: *in vitro* fertilization (IVF), non-IVF fertility treatment (NIFT), or spontaneous pregnancies.

Interventions—None

Outcome Measure—The main outcome was presence of true SMM, such as eclampsia, respiratory failure, and peripartum hysterectomy. Deliveries were screened using 1) ICD-9 codes,

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2) prolonged postpartum stay, 3) maternal ICU admissions, and 4) blood transfusion. The charts of women meeting the screening criteria were reviewed to identify true SMM based on a previously validated method, recognizing that medical record review is the gold standard.

Results—Of the 6543 deliveries, 246 (3.8%) were IVF conceptions and 109 (1.7%) NIFT conceptions. Sixty nine (1.1%) cases of true SMM were identified. In multivariate analyses, any fertility treatment (IVF + NIFT) was associated with increased risk of SMM compared to spontaneous conceptions (OR 2.40, 95%CI 1.10–5.23). In a subset analysis of singletons only, the association between any fertility treatment (IVF + NIFT) and SMM was not statistically significant (OR 2.11, 95% CI 0.83–5.37, P=0.12).

Conclusions—Overall, fertility treatment increased risk for SMM events. Given the limited sample size, the negative finding with singleton gestations is inconclusive. Larger multi-center studies with accurate documentation of fertility treatment and SMM cases are needed to further clarify the risk associated with singletons.

Keywords

fertility; infertility; in vitro fertilization; severe maternal morbidity

Introduction

Severe maternal morbidity (SMM) is on the rise in the United States, with 158 cases for every 10,000 delivery hospitalizations per year (1). This estimate is a 75% increase compared to twenty years ago (1), leading to a national effort to standardize the review of SMM cases with the goal of quality improvement in maternal care (2, 3). True examples of SMM include, but are not limited to, eclampsia, respiratory failure, and peripartum hysterectomy. Various criteria have been proposed to define SMM cases, including 1) maternal intensive care unit (ICU) admission or transfusion of ≥4 units of blood products (4, 5), 2) utilization of CDC ICD-9 codes associated with maternal morbidity and mortality (1, 6), and 3) most recently, a clinical gold standard used to validate relevant CDC ICD-9 codes (7). Three of the known risk factors for SMM, older age, multiple birth, and cesarean delivery (8), are associated with fertility treatment, which has also been on the rise over the last few decades.

Although much attention has focused on adverse perinatal outcomes of children conceived by fertility treatment (9–12), maternal outcomes have received less attention. Studies have linked *in vitro* fertilization (IVF) with adverse obstetric outcomes such as placenta previa (13, 14), placenta abruption (13), and pre-eclampsia (13, 15, 16). To date, there are two recent studies that examined whether these associations translate into increased SMM, which concluded that singleton pregnancies conceived with assisted reproductive technology (ART) had a twofold increased risk of SMM (17, 18). However, both of these studies utilized only CDC ICD-9 codes to identify SMM cases, which have a low positive predictive value of 0.44 when validated with medical record review (7).

In our study, we aimed to determine whether pregnancies conceived by fertility treatment had an increased risk of true SMM, based on CDC ICD-9 codes in conjunction with the gold

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standard of medical record review, compared to pregnancies conceived spontaneously. In addition, we are the first study to include both IVF and non-IVF fertility treatment (NIFT) pregnancies. IVF is the mainstay of ART and primarily involves the fertilization of oocytes with sperm in a laboratory procedure and subsequent embryo transfer into the uterus. ART and IVF are terms that are often used interchangeably. NIFT consists of various other medical interventions that include ovarian stimulation with pharmacologic agents such as selective estrogen receptor modulators, aromatase inhibitors, gonadotropins, with or without intrauterine inseminations (IUIs).

We hypothesized that the increased risk of SMM associated with fertility treatment can be explained by factors by confounders, such as maternal age and multiple births, as opposed to an independent association with IVF and NIFT treatment.

Materials and Methods

In this retrospective cohort study, we reviewed the charts of all live births >20 weeks gestation at our center from January 1, 2012 through December 31, 2012 under an IRB approved protocol. Data from electronic medical records were abstracted for mode of conception (IVF, NIFT, or spontaneous) by extensive review of records associated with obstetric inpatient care at the time of delivery, including scanned prenatal records, hospital admission notes, and discharge summaries. The scanned prenatal record was found to be the most common source for fertility treatment information at our institution. Providers annotated the prenatal records with notations such as “IVF”, “clomiphene citrate”, or “intrauterine inseminations”. Preconception and prenatal care records, including genetic counseling notes and actual fertility treatment processes, were available in the electronic medical records for only a subset of patients (<50%). We did not review treatment records from outside fertility clinics. Pregnancies in which fertility treatment was not specified were presumed to be spontaneous conceptions.

Covariate data including maternal age, body mass index, multifetal pregnancy, preterm delivery, and delivery method were abstracted from the electronic medical record. Race/ethnicity, insurance (government or private), and co-morbidities present on admission (coronary heart disease, pre-gestational or gestational diabetes mellitus, chronic or gestational hypertension) were variables obtained from our institution’s quarterly submission to the California Office of Statewide Health Planning and Development. Government versus private insurance was used as a surrogate marker for socioeconomic status.

The primary outcome was presence of true SMM. We identified true SMM cases based on the Gold Standard Severe Maternal Morbidity Case Review Guidelines as previously described (7). Briefly, all deliveries were initially screened using four strategies: 1) CDC ICD-9 diagnosis and procedure codes, 2) prolonged postpartum length of stay (>4 days for a vaginal delivery or 6 days for a cesarean delivery), 3) any maternal ICU admission, and 4) blood transfusion. The charts of women who screened positive were subsequently reviewed in detail to determine if true SMM was present based on the Gold Standard Guidelines

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(S.J.K, N.G.) given that the positive predictive value based on CDC ICD-9 codes is only 0.44 (7).

The Gold Standard Guidelines were developed by a team of 10 obstetric researchers experienced in quality reviews (7). The team first developed a set of consensus clinical conditions establishing a “gold standard” to identify true SMM. Consensus was developed using 4 rounds of a modified Delphi approach. To build consistency among reviewers, a series of 30 case scenarios were created to explore borderline situations. These guidelines provided specific examples of true SMM in categories of hemorrhage, hypertension/neurologic, renal, sepsis, pulmonary, cardiac, ICU/invasive monitoring, surgical, bladder, and bowel complications, and anesthesia complications (7). To illustrate this point, a maternal ICU admission due to respiratory distress with intubation would be classified as a true SMM based on the Gold Standard Guidelines after medical record review, whereas an uneventful ICU admission for observation due to a previous history of peripartum cardiomyopathy would be a false positive identified by the screening criterion of any ICU admission. Categories of true SMM include cardiovascular disease, hypertension, obstetrical hemorrhage (atony, vaginal laceration), placental hemorrhage (bleeding from a placenta previa or accreta), and other. In this study, 175 charts screened positive for SMM, and 69 subsequently fulfilled criteria for true SMM.

Univariate analyses were performed using standard descriptive statistics. Multivariate logistic regression analyses, adjusted for maternal age (continuous variable), race (four categories and White/Non-White), BMI (three categories 18.5–24.9, 25–29.9, ≥30 kg/m^2), insurance (private/government), and presence of co-morbidities (CHD, diabetes mellitus, and hypertension), were performed to determine the association between any fertility treatment (IVF + NIFT) and SMM. As multiple gestations may be on the causal pathway between fertility treatment and SMM, a subset analysis was performed for singleton gestations only. Statistical significance was set at $P<0.05$. Data analyses were performed using SAS (version 9.3, SAS Institute Inc., Cary, NC).

Results

During the time period of January 2012 to December 2012, there were 6543 deliveries at Cedars-Sinai Medical Center, of which 246 (3.8%) were documented IVF conceptions and 109 (1.7%) NIFT conceptions. Sixty-nine cases (1.1%) of true SMM were identified – 59 spontaneous conceptions, 3 NIFT conceptions, and 7 IVF conceptions. Baseline demographics of the cohort are presented in Table 1. Non-White race ($P=0.001$), multifetal pregnancy ($P<0.001$), mode of conception ($P=0.004$), preterm delivery ($P<0.001$), cesarean delivery ($P<0.001$), type of health insurance ($P<0.001$), and the presence of coronary heart disease ($P<0.001$), diabetes mellitus ($P=0.03$), and hypertension ($P=0.03$) were associated with SMM in univariate analyses.

Of SMM cases, obstetrical hemorrhage (ie. atony, vaginal laceration) was the most common cause, accounting for almost 50% of our cases (Table 2). Other primary diagnoses fulfilling the criteria for SMM included cardiovascular disease (4.3%), hypertensive disorders (17.4%), and placental hemorrhage (ie. bleeding from a placenta previa or accreta) (17.4%).

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In adjusted logistic regression analyses, any fertility treatment (IVF + NIFT) demonstrated a significantly increased risk of SMM compared to spontaneous conceptions (OR 2.40, 95% CI 1.10–5.23, P=0.03). In a subset analysis of singletons only (N=6377), there were 62 true SMM cases – 55 spontaneous conceptions, 3 NIFT conceptions, and 4 IVF conceptions. Among singletons, the association between any fertility treatment (IVF + NIFT) and SMM was not statistically significant (OR 2.11, 95% CI 0.83–5.37, P=0.12).

Discussion

Our results indicate that any fertility treatment (IVF + NIFT) is associated with an increased risk of SMM in analyses adjusted for maternal age, race, obesity, insurance, and comorbidities. Given the limited sample size, the negative finding with singleton gestations is inconclusive.

Fertility treatment has been shown to be associated with adverse obstetric outcomes. One study from Japan concluded that ovarian stimulation, IUI, and IVF are all associated with a higher risk of placenta previa and preterm delivery, whereas only IVF was associated with a higher risk of emergency cesarean delivery and postpartum hemorrhage, compared to controls (19). We previously demonstrated that there is an increased risk of retained placenta in very advanced maternal age women who conceive with IVF, suggesting that placentation abnormalities may contribute to maternal morbidity (20). Another study from Australia demonstrated adverse obstetric outcomes in subfertile women conceiving without IVF, which presumably included women using NIFT treatments however this was not documented (21).

The main strength of our study is the systematic definition of true SMM, a compilation of adverse obstetric outcomes, which resulted in a 1.1% prevalence of SMM cases consistent with the national average (1). This is the first study examining the association between fertility treatment and true SMM. We compare our study conclusions to a recent study by Martin et. al. which demonstrated that singleton pregnancies conceived by ART were at an increased risk for SMM between 2008–2012 (17). Martin et. al. identified SMM cases based on CDC ICD-9 codes (1), which have been previously shown to have a false positive rate of almost 60% (7). Furthermore, Martin et. al. reported an SMM rate of 399 cases per 10,000 singleton deliveries between 2008–2012 (17), which is more than twice the previously reported numbers for SMM cases cased on the same diagnostic criteria (158 cases per 10,000 hospitalization deliveries in 2008–2009) (1). Our study utilizes the gold standard to identify true SMM cases based on extensive chart review, which demonstrated that only 39% of cases that screened positive were true SMM cases (69/175). Our study did not show an increased risk of true SMM associated with fertility treatment among the subset of singleton gestations; however, the limited sample size precludes a conclusive negative finding.

Although larger multi-center studies are needed, our center has a patient population enriched for fertility treatment. Compared to the national average of 1.5% IVF conceptions, the higher prevalence of IVF conceptions (3.8%) at CSMC reflects our unique patient population and the fact that California has the highest number of ART centers, ART procedures performed, and live-birth deliveries in the US (22). Although our intention was

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to include all NIFT conceptions, we recognize that NIFT conceptions are notoriously under-reported and misclassification is a possibility in our study. Mathematical models have proposed that NIFT accounts for approximately 4.6% of infants born in the US (23) and contributes significantly to the incidence of multiple births, especially higher order multiples (24). In our study, NIFT use was indicated in 1.7% of charts reviewed, lower than expected, and may suggest misclassification as a possibility and may bias our results toward the null hypothesis. This underscores the urgent need for improved documentation on fertility and details of fertility treatment on a national level. Existing methods of reporting fertility treatment on birth certificates are inadequate, with some studies demonstrating that the sensitivity of reporting IVF was less than 30% (25, 26).

Another limitation of our study, as with all studies investigating the association of fertility treatments with maternal and fetal outcomes, is our inability to distinguish associations due to the actual treatments and procedures from those due to the underlying etiology of infertility. We also do not have details regarding specific IVF procedures such as intracytoplasmic sperm injection, use of frozen embryos, or embryo biopsy for preimplantation genetic screening. Our results need to be further corroborated as this was a single-institution study and the low incidence of SMM. With multi-center studies and a larger sample size of SMM cases, we may be able to further determine whether the specific procedures of IVF or NIFT and etiology for infertility are associated with SMM independent of multiple gestations.

In conclusion, fertility treatment (IVF and NIFT) is associated with an increased risk of true SMM as defined by the gold standard of medical record review. Larger multi-center studies with accurate documentation of fertility treatment and true SMM cases are needed to further clarify the risk associated with singletons.

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Table 1

Baseline Characteristics of the Maternal Cohort

	SMM N=69	No SMM N=6474	P-value
Maternal Age, years	34.0 (6.7)	32.9 (5.30)	0.18
Maternal Race, n(%)			0.001
White	36 (52.2)	4541 (70.5%)	
Black	14 (20.3)	590 (9.2)	
Asian	14 (20.3)	798 (12.4)	
Other	5 (7.3)	512 (8.0)	
Body Mass Index, kg/m^2			0.50
18.5–24.9	9 (13.6)	1220 (18.9)	
25–29.9	29 (43.9)	3021 (46.8)	
≥30	28 (42.4)	2012 (34.3)	
Multifetal pregnancy, n(%)	7 (10.1)	159 (2.5)	<0.001
Mode of conception, n(%)			0.004
IVF	7 (10.1)	239 (3.7)	
NIFT	3 (4.4)	106 (1.6)	
Spontaneous	59 (85.5)	6129 (94.7)	
Preterm Delivery <37 weeks, n(%)	25 (36.8)	470 (7.4)	<0.001
Cesarean Delivery, n(%)	55 (79.7)	2338 (36.1)	<0.001
Health Insurance, n(%)			<0.001
Government	20 (29)	831 (13)	
Private	49 (71)	5583 (87)	
Co-morbidities, n(%)			
Coronary Heart Disease	5 (7)	26 (0.4)	<0.001
Diabetes Mellitus	10 (15)	455 (7)	0.03
Hypertension	3 (4)	57 (1)	0.03

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Table 2

True SMM Cases represented in the Maternal Cohort

	Spontaneous N=59	NIFT N=3	IVF N=7
Obstetrical Hemorrhage, n(%)	29 (49)	1 (33)	4 (57)
Placental Hemorrhage, n(%)	10 (17)	1 (33)	1 (14)
Hypertensive Disorders, n(%)	9 (15)	1 (33)	2 (29)
Cardiovascular Disease, n(%)	3 (5)	–	–
Other, n(%)	8 (14)	–	–