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Impact of fertility treatment on severe maternal morbidity

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Objective: To determine if fertility treatment is associated with increased risk of severe maternal morbidity (SMM) compared with spontaneous pregnancies.
Design: Retrospective cohort study.
Setting: Academic medical center.
Patient(s): In 2012, 6,543 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.
Intervention(s): None.
Main Outcome Measure(s): The main outcome was presence of true SMM, such as eclampsia, respiratory failure, and peripartum hysterectomy. Deliveries were screened with the use of: 1) International Classification of Diseases 9 codes; 2) prolonged postpartum stay; 3) maternal intensive care unit 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 criterion standard.
Result(s): Of the 6,543 deliveries, 246 (3.8%) were IVF conceptions and 109 (1.7%) NIFT conceptions. Sixty-nine cases of true SMM were identified (1.1%). In multivariate analyses, any fertility treatment (IVF + NIFT) was associated with increased risk of SMM compared with spontaneous conceptions. In a subset analysis of singletons only, the association between any fertility treatment (IVF + NIFT) and SMM was not statistically significant.
Conclusion(s): Overall, fertility treatment increased risk for SMM events. Given the limited sample size, the negative finding with singleton gestations is inconclusive. Larger multicenter studies with accurate documentation of fertility treatment and SMM cases are needed to further clarify the risk associated with singletons. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Fertility, infertility, in vitro fertilization, severe maternal morbidity

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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 represents a 75% increase from 20 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) use of Centers for Disease Control and Prevention International Classification of Diseases 9 (ICD-9) codes associated with maternal morbidity and mortality (1, 6); and 3) most recently, a clinical criterion standard used to validate relevant 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 past 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 obstetrical outcomes such as placenta previa (13, 14), placenta abruption (13), and preeclampsia (13, 15, 16). To date, there are two recent studies examining 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 used only 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 the present study, we aimed to determine whether pregnancies conceived with the use of fertility treatment had an increased risk of true SMM, based on ICD-9 codes in conjunction with the criterion standard of medical record review, compared with pregnancies conceived spontaneously. In addition, this is 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, and gonadotropins, with or without intrauterine insemination (IUI).

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

MATERIALS AND METHODS

In this retrospective cohort study, we reviewed the charts of all live births after 20 weeks of gestation at our center from January 1, 2012, through December 31, 2012, under an Institutional Review Board–approved protocol. Data from electronic medical records were abstracted for mode of conception (IVF, NIFT, or spontaneous) by means of extensive review of records associated with obstetrical 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 "IUI." 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 comorbidities present on admission (coronary heart disease, pregestational 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 with the use of 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 as positive were subsequently reviewed in detail to determine if true SMM was present based on the Gold Standard Guidelines (S.J.K, N.G.) given that the positive predictive value based on ICD-9 codes is only 0.44 [7].

The Gold Standard Guidelines were developed by a team of ten obstetrical 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 because of 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 with the use of standard descriptive statistics. Multivariate logistic regression analyses, adjusted for maternal age (continuous variable), race (four categories and white/nonwhite), BMI (three categories: 18.5–24.9, 25–29.9, and ≥ 30 kg/m^2), insurance (private/government), and presence of comorbidities (coronary heart disease, diabetes mellitus, and hypertension), were performed to determine the association between any fertility treatment (IVF + NIFT) and SMM. Because 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 $P < .05$. Data analyses were performed with the use of SAS (version 9.3; SAS Institute).

RESULTS

During the time period of January 2012 to December 2012, there were 6,543 deliveries at Cedars-Sinai Medical Center, of which 246 (3.8%) were documented IVF conceptions and 109 (1.7%) NIFT conceptions. Sixty-nine cases of true SMM were identified (1.1%): involving 59 spontaneous conceptions, 3 NIFT conceptions, and 7 IVF conceptions. Baseline