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Severe Maternal Morbidity and the Use of Assisted Reproductive Technology in Massachusetts

Candice Belanoff, ScD, MPH¹, Eugene R. Declercq, PhD¹, Hafsatou Diop, MD, MPH², Daksha Gopal, MPH¹, Milton Kotelchuck, PhD, MPH³, Barbara Luke, ScD, MPH⁴, Thien Nguyen, MPH¹, and Judy E. Stern, PhD⁵

¹Department of Community Health Sciences, Boston University School of Public Health, Boston, MA

²Massachusetts Department of Public Health, Boston, MA

³Massachusetts General Hospital, Center for Child & Adolescent Health Research and Policy, Harvard Medical School, Boston, MA

⁴Department of Obstetrics, Gynecology, and Reproductive Biology, Michigan State University, East Lansing, MI

⁵Department of Obstetrics & Gynecology, Geisel School of Medicine at Dartmouth, Lebanon, NH

Abstract

Objectives—To assess whether risk of severe maternal morbidity at delivery differed for women who conceived using assisted reproductive technology (ART), those with indicators of subfertility but no ART (“subfertile”), and those who had neither ART nor subfertility (“fertile”).

Methods—This retrospective cohort study was part of the larger Massachusetts Outcomes Study of Assisted Reproductive Technology (MOSART). To construct the MOSART database and identify ART deliveries, we linked ART treatment records to birth certificates and maternal and infant hospitalization records occurring in Massachusetts between 2004 and 2010. An algorithm of ICD-9-CM diagnosis and procedure codes identified severe maternal morbidity. We used Logistic Generalized Estimating Equations to estimate odds of severe maternal morbidity associated with fertility status, adjusting for maternal demographic and health factors and gestational age, stratifying on plurality and method of delivery.

Results—The prevalence of severe maternal morbidity among this population (n = 458,918) was 1.16%. The overall, crude prevalences of severe maternal morbidity among fertile, subfertile and ART deliveries were 1.09%, 1.44% and 3.14%, respectively. The most common indicator of severe maternal morbidity was blood transfusion. In multivariable analyses, among singletons, ART was associated with increased odds of severe maternal morbidity compared to both fertile

Corresponding Author: Candice Belanoff, ScD, MPH, Department of Community Health Sciences, Boston University School of Public Health, 801 Massachusetts Avenue, Room 429, Boston, MA 02118, cbelanof@bu.edu, 617-414-1441.

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(Vaginal: aOR 2.27, 95% CI: 1.78 – 2.88; cesarean: aOR 1.67, 95% CI: 1.40 – 1.98, respectively) and subfertile (vaginal: aOR 1.97, 95% CI: 1.30 – 3.00; cesarean: aOR 1.75, 95% CI: 1.30 – 2.35, respectively) deliveries. Among twins, only cesarean ART deliveries had significantly greater severe maternal morbidity compared to cesarean fertile deliveries (aOR 1.48, 95% CI: 1.14, 1.93).

Conclusions—Women who conceive through ART may have elevated risk severe maternal morbidity at delivery, largely indicated by blood transfusion, even when compared with a subfertile population. Further research should elucidate mechanisms underlying this risk.

INTRODUCTION

The rate of pregnancy-related death in the United States has been on the rise since the 1980's, increasing from 7.2 per 100,000 in 1987 to 17.8 in 2011.¹ However, because mortality is so rare, surveillance efforts have also targeted severe maternal morbidity (SMM), defined as having any of twenty-five ICD-9 hospitalization codes for procedures and conditions indicating a potentially life threatening situation.² The SMM rate more than doubled in the United States between 2001 and 2011, increasing from 78.6, to 162.8 per 10,000 delivery hospitalizations.² During the same period, the proportion of infants born as a result of assisted reproductive technology (ART), defined as “fertility treatments in which both eggs and embryos are handled in the laboratory,”³ increased from 0.9% to 1.5%.^{3,4}

While the profile of the ART patient population tends to reflect greater social advantage and factors protective against SMM than the general maternity population,⁵ ART has been associated with known risk factors for SMM including placenta accreta,⁶ plural births⁷ and cesarean delivery.⁸ Furthermore, women who use ART to conceive are more likely to have underlying health and fertility problems which necessitated the use of ART.^{9,10} As a result, previous research has encountered difficulty in distinguishing the direct effects of ART on maternal outcomes from other contributing health issues.¹¹ The objective of this analysis was to examine whether ART use contributed to the frequency and type of severe maternal morbidities at the time of delivery apart from maternal fertility status and other health factors.

MATERIALS AND METHODS

This is one in a series of retrospective cohort analyses evaluating the effect of maternal fertility status (subfertile women treated with ART, subfertile women not treated with ART, and fertile women) on the course and outcome of pregnancy. This analysis is part of a larger population-based study of ART in Massachusetts.^{9,10,12-16} The project known as the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) took place under a Memorandum of Understanding for use of the SART CORS data and was approved by Institutional Review Boards of Boston University, the Massachusetts Department of Public Health (MDPH), all investigator institutions, and by the SART Research Committee.

Data for these analyses were obtained from two sources 1) the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) online database and 2) the birth certificates, fetal death records, and hospital utilization data in the Massachusetts-based Pregnancy to Early Life Longitudinal (PELL) Data System.¹⁷

SART CORS is a clinic and treatment-based data system that contains cycle-based ART data from more than 90% of United States ART clinics and over 97% of ART cycles.⁷ SART CORS data contain patient demographics (age, race, diagnosis), ART treatment data (fresh versus frozen state, oocyte type, micromanipulation procedures and embryos transferred) and outcome data (cancellation, pregnancy, live birth, birth outcomes) on all cycles of ART at participating clinics and data from this system are available for research from 2004 onward. All Massachusetts clinics report their data to SART CORS.

PELL is a relational data system composed of individual databases linked together by randomly-generated unique IDs for mother and infant. The linked database contains information on more than 99% of all births and fetal deaths in Massachusetts from 1998-2010 and links these to corresponding hospital utilization data (hospital admissions, observational stays, and emergency room visits) for individual women and their children. MDPH and the Massachusetts Center for Health Information and Analysis are the custodians of the PELL data.

The construction of the MOSART database involved a linkage of the SART CORS and PELL data systems for all deliveries to Massachusetts residents in Massachusetts hospitals between July 1, 2004 and December 31, 2010. In order to capture births plausibly attributable to ART treatment cycles beginning on January 1, 2004, we included births occurring from July 1, 2004, through December 31, 2010, the last date that birth records were available to us at the time. A detailed description of the PELL and SART CORS data, their linkage and validation have been published previously.¹⁴ PELL records were matched against eligible ART treatment cycle records – those occurring to Massachusetts resident women or to women who obtained treatment in a Massachusetts clinic during the same timeframe (43,214 eligible cycles for 17,547 women). Among our total sample of PELL deliveries, 13,981 (2.70%) linked to ART treatment cycles in SART CORS, indicating that these infants were conceived using ART. We limited our analysis to singleton or twin deliveries and excluded deliveries with incomplete data on the key predictors or outcomes of interest and those to women under age eighteen.

An algorithm was developed to identify deliveries to women with indicators of subfertility who did not use ART to become pregnant.¹⁰ Briefly, subfertile deliveries were identified using three sources: (1) birth certificate items indicating the use of fertility treatment for the current, or a prior pregnancy within the past five years; (2) hospital contact within five years prior to the current pregnancy for a condition specifically related to infertility (ICD-9 codes 628.0, 628.2, 628.3, 628.8, 628.9, V230); or (3) an ART treatment cycle for a *prior* pregnancy attempt occurring after January 1, 2004 but no ART cycle linked to the index delivery, as reported to SART CORS. From the pool of deliveries that met at least one of these criteria, we eliminated ART-assisted deliveries identified in the SART CORS database in the study period and duplicate cases which resulted in 8,984 non-ART singleton or twin deliveries between July 1, 2004 and December 31, 2010 to women with at least one indicator of subfertility.

The Centers for Disease Control and Prevention defines severe maternal morbidity using delivery hospitalization data and International Classification of Diseases, Ninth Revision,

Clinical Modification (ICD-9-CM) diagnosis and procedure codes that indicate a potentially life-threatening maternal condition or complication.¹⁸ Delivery hospitalizations with severe maternal morbidities were identified using a published algorithm that includes 25 specific ICD-9-CM diagnosis and procedure codes (Table 1) with indicators of organ-system failure that likely represent specific well-defined severe events.² Irrespective of the pregnancy outcome, women who had any ICD-9-CM codes that indicate such a potentially severe event were designated as having severe maternal morbidity.² We applied this algorithm to all deliveries occurring at 20 weeks or greater gestational age in our study population, and evaluated the differences by maternal fertility group and plurality. The primary outcome measure was severe maternal morbidity (SMM), defined as any of the 25 factors listed in Table 1.²

To estimate the association of ART with risk of any severe maternal morbidity during the delivery hospitalization, we analyzed the data using Logistic Generalized Estimating Equations (GEE). The GEE model accounted for correlation between multiple infants born to the same woman during the time period studied, as there were women who had more than one delivery in the MOSART data system. Because of the known maternal health risks associated with both plurality and cesarean delivery,^{17;19} and the association of these with fertility treatment, models were run separately for singleton and twin pregnancies, and for vaginal and cesarean deliveries.

We tested potential confounders of the association between fertility status of the delivery and subsequent SMM. The final model included maternal age, education, race and ethnicity, marital status, payer for delivery, smoking during pregnancy, parity, and gestational or chronic hypertension or diabetes. In order to further adjust for the potentially confounding effects of certain maternal health conditions, our models also included selected obstetric or gynecologic health conditions found in the hospital discharge records and known to be associated with infertility including endometriosis, pelvic inflammatory disease, polycystic ovarian syndrome, intrauterine synchia, peritoneal adhesions, abdominal/ovarian/tubal pregnancy, and absence of menstruation and combined these into a single dichotomous measure as selected OB GYN conditions.²⁰ We tested for interaction effects between the main independent variable (fertility and treatment status of the delivery) and select demographic characteristics, (e.g. maternal age and race and ethnicity), associated with each of the perinatal outcomes. We examined the Type 3 analysis of effects for significance, finding no set of interaction terms meeting the criterion of $p < 0.05$.

We performed a count of the most common severe morbidities reported on maternal hospital discharge records and calculated the proportion of all deliveries affected by a given morbidity, reporting those which were most prevalent, by fertility status, plurality, and method of delivery. Finally, because blood transfusion was found to be the most common indicator of severe morbidity, we performed a post-hoc analysis examining the prevalence of transfusion within the ART group, across diagnoses recorded in SART CORS. Diagnoses tested included uterine factor, diminished ovarian reserve, endometriosis, male factor, ovulatory disorder, other factors, tubal factor, and unknown factors. The data were analyzed using SAS software version 9.2 (SAS Institute Inc., Cary, NC, USA.)

RESULTS

Out of a total of 474,482 deliveries occurring between July 1, 2004 and December 31, 2010 in Massachusetts and included in the MOSART database 458,918 (96.7%) were born to mothers 18 or older, were live-born singletons or twins, and had complete data on the variables of interest (Figure 1). A description of the study population by fertility status group and plurality is shown in Table 2. Women who underwent ART, those with subfertility who did not undergo ART, and those in the fertile group differed significantly on multiple socio-demographic and health characteristics. Compared to the fertile group, the ART and subfertile groups were more likely to be over 40 (20.6% and 14.8% vs 3.7%) white, (85.2% and 84.6% vs 67.1%) and to have private health insurance at the time of delivery (95.0% and 90.4% vs 57.9%). Women in the ART and subfertile groups were also more likely to have delivered twins (26.0% and 8.3% vs 1.4%), have a preterm birth (21.7% and 11.7% vs 6.9%), and a Cesarean delivery 54.2% and 45.3% vs 31.3%). All demographic comparisons across the three groups were significant at a level of $p < 0.001$.

Among our total study population, we identified 5,318 deliveries (1.16%) which involved an SMM. The overall prevalences of SMM among fertile, subfertile and ART deliveries were 1.09%, 1.44% and 3.14%, (data not shown). Among women with singleton pregnancies, those with cesarean and ART combined had a significantly higher rate of SMM compared to women with cesarean and subfertile (OR 1.84, 95% CI 1.37-2.46) or cesarean and fertile deliveries (OR 1.65, 95% CI 1.40-1.94) with crude prevalences being 3.37% versus 1.86% and 2.07% respectively, (Table 3). In the adjusted analysis, cesarean ART deliveries had 1.75 times higher odds (95%CI 1.30-2.35) compared to cesarean subfertile deliveries and 1.67 times higher odds of SMM (95%CI 1.40-1.98) compared to cesarean fertile deliveries. Among women with singletons who delivered vaginally, ART pregnancies had the highest proportion of any severe morbidity compared with subfertile (OR 2.21 95%CI 1.46-3.36) and fertile deliveries (OR 2.46 95%CI 1.96-3.09) with crude prevalences being 1.44%, versus 0.65% and 0.59%, respectively. In the adjusted analysis, women with ART who delivered vaginally had 1.97 times higher odds (95%CI 1.30-3.00) than women with subfertile deliveries and 2.27 times higher odds of SMM (95%CI 1.78-2.88) than those with fertile deliveries.

Twin deliveries were associated rates of SMM ranging from 3.94% among fertile, vaginal deliveries, to 5.76% among ART, cesarean deliveries. Among twin deliveries, the only difference in SMM was found between ART and fertile cesarean groups (aOR 1.48, 95% CI: 1.14 – 1.93). The subfertile group did not differ significantly from a fertile group in any model.

The most common indicator of SMM across all deliveries, and for each subgroup, was blood transfusion, ($n = 3,466$, 0.76%), involved in nearly two thirds of all SMM cases. Prevalence of transfusion varied across the groups, with ART cesarean twin deliveries having the highest (4.03%) and vaginal singleton deliveries to fertile women the lowest (0.42%) transfusion rates. (Data not shown)

We examined hospital discharge records post-hoc to see what other conditions accompanied transfusions and found that almost 90% of deliveries that involved a transfusion also had an indication of a hemorrhagic or anemic condition (data not shown). We also sub-categorized ART deliveries by those involving male infertility, female infertility, both male and female infertility, and unexplained infertility to examine whether maternal and/or paternal factors were associated with increased risk of SMM and found no significant differences (data not shown). When we calculated the prevalence of transfusion by specific infertility diagnoses recorded in SART CORS, only women with “uterine factor” had a significantly higher prevalence of transfusion than those without, however, only 16 (5.3%) of the 300 transfusion cases were affected by uterine-factors, (data not shown).

DISCUSSION

Women who conceived using ART and delivered singleton infants were significantly more likely than women with subfertile and fertile deliveries to suffer a severe morbidity regardless of method of delivery and adjusting for demographic and health factors. The risk of SMM in women with singleton subfertile births did not differ significantly from that of the fertile group. Among twin deliveries, there were fewer significant differences, perhaps owing to smaller numbers and the higher occurrence of maternal morbidities associated with plural births in general.¹⁹ It should be noted, however, that the absolute increase in risk associated with ART was very small, under 2 percentage points, for all sub-group comparisons.

The overall prevalence of SMM among Massachusetts mothers (1.16%) in this study, was consistent with previously reported national estimates for similar time periods. Using a national sample, Kuklina et al. found a SMM prevalence of 0.81% in 2004–05²¹ and Callaghan et al. found 1.29% in 2008-2009.² The most common indicator of a SMM event in our sample, as in these previous studies, was blood transfusion, which largely accounted for greater SMM observed among the ART groups. However, no distinct co-morbidity patterns were observed that would explain the higher transfusion rates. Rates of blood transfusion are dependent at least in part on guidelines around acceptable maternal hemoglobin levels, and these guidelines have changed over time.²⁷ Therefore, studies of SMM, particularly time trend analyses should be mindful of changes in practice standards for management of hemorrhage and anemia in obstetric patients.

This study of the association of ART with SMM is important for its inclusion of a non-ART but subfertile comparison group¹⁰. A Dutch study found 2.5 times greater risk of SMM among ART compared to fertile births, though the researchers did not include a subfertile comparison group.²² A study by Silberstein, et al. compared the risks of certain severe adverse outcomes among groups with ART, non-ART ovulation induction and spontaneous conceptions, observing a significant trend of highest to lowest risk across the three groups, respectively.²³ We observed comparable trends across our three comparison groups.

The MOSART database allowed us to identify infants conceived with ART, and distinguish them from non-ART, subfertile pregnancies. Additionally, this population-level database included nearly all births to women 18 and older in Massachusetts over more than a 6 year

period. Our stratification by plurality and method of delivery, and comparison of ART to subfertile deliveries allowed us to account for the higher prevalence of cesarean and plural births among ART pregnancies,^{17:19} and estimate the contribution of ART to severe morbidity apart from underlying health issues and complications more common to ART pregnancies. This approach addressed a common limitation of prior ART studies.¹⁰

One study limitation was the lack of information on non-ART fertility treatments in the subfertile group. Therefore, we could not distinguish all sub-types of subfertile pregnancies. In addition, some subfertile deliveries may have been misclassified as “fertile,” though this is unlikely to have affected the much larger fertile group. Similarly, some women who delivered in Massachusetts may have received ART out of state and thus would be misclassified as fertile or subfertile. Similarly, we could not determine whether events possibly accompanying ART such as gonadotropin medications and fetal losses contributed to the greater observed SMM. Lastly, our analysis of only Massachusetts births may raise concerns around generalizability, however our findings largely corresponded to previous national data on the nature and prevalence of SMM by fertility groups, as noted above, suggesting that they may well translate to other settings.

In conclusion, women who conceived via assisted reproductive technology and delivered singleton infants were found to be at elevated risk of severe morbidities during their delivery hospitalizations compared to women who had indicators of subfertility but did not use ART to conceive, to women who had neither indicators of subfertility nor ART. Blood transfusion was the most common indicator of a severe morbid event for all deliveries, however, further research is needed toward understanding mechanisms and accompanying conditions which may underlie the elevated risk of severe morbidity among women who undergo ART.

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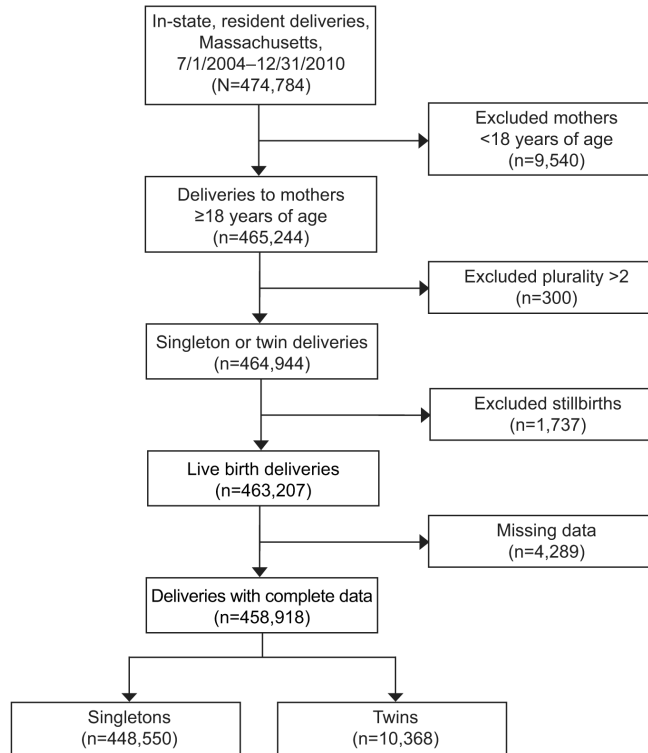


Figure 1.
Flow chart of study population selection.

Table 1Severe Maternal Morbidity Indicators and Corresponding ICD-9-CM Codes^{1,2}

Severe Maternal Morbidity Indicator	ICD-9-CM Codes	ICD-9-CM Diagnosis Code	ICD-9-CM Procedure Code
1. Acute myocardial infarction	410.xx	x	
2. Acute renal failure	584.x, 669.3x	x	
3. Adult respiratory distress syndrome	518.5, 518.81, 518.82, 518.84, 799.1	x	
4. Amniotic fluid embolism	673.1x	x	
5. Aneurysm	441.xx	x	
6. Cardiac arrest/ventricular fibrillation	427.41, 427.42, 427.5	x	
7. Disseminated intravascular coagulation	286.6, 286.9, 666.3x	x	
8. Eclampsia	642.6x	x	
9. Heart failure during procedure or surgery	669.4x, 997.1	x	
10. Internal injuries of thorax, abdomen, and pelvis	860.xx—869.xx	x	
11. Intracranial injuries	800.xx, 801.xx, 803.xx, 804.xx, 851.xx-854.xx	x	
12. Puerperal cerebrovascular disorders	430, 431, 432.x, 433.xx, 434.xx, 436, 437.x, 671.5x, 674.0x, 997.2, 999.2	x	
13. Pulmonary edema	428.1, 518.4	x	
14. Severe anesthesia complications	668.0x, 668.1x, 668.2x	x	
15. Sepsis	038.xx, 995.91, 995.92	x	
16. Shock	669.1x, 785.5x, 995.0, 995.4, 998.0	x	
17. Sickle cell anemia with crisis	282.62, 282.64, 282.69	x	
18. Thrombotic embolism	415.1x, 673.0x, 673.2x, 673.3x, 673.8x	x	
19. Blood transfusion	99.0x		x
20. Cardio monitoring	89.6x		x
21. Conversion of cardiac rhythm	99.6x		x
22. Hysterectomy	68.3x-68.9		x
23. Operations on heart and pericardium	35.xx, 36.xx, 37.xx, 39.xx		x
24. Temporary tracheostomy	31.1		x
25. Ventilation	93.90, 96.01-96.05, 96.7x		x

Note: ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification

Table 2

Description of the Study Population* (Massachusetts births, July 1, 2004 – December 31, 2010)

Characteristics	ART	Subfertile	Fertile
Total (deliveries)	13,677	8,754	436,487
Mother's age (%)			
<30	8.3	11.9	47.5
30-39	71.1	73.3	48.8
40+	20.6	14.8	3.7
Mother's race and ethnicity (%)			
Non-Hispanic Black	3.1	3.1	8.9
Non-Hispanic White	85.2	84.6	67.1
Hispanic	3.5	4.4	14.2
Asian/Pacific Islander	7.2	6.8	7.7
American Indian/Alaskan Native	1.0	1.1	2.1
Mother's education (%)			
<=High School	9.2	11.9	36.5
Some post-High School	15.6	17.6	21.9
Bachelor's degree or greater	75.2	70.6	41.6
Unmarried (%)	4.1	5.6	33.6
Private health insurance (%)	95.0	90.4	57.9
Primiparous (%)	54.6	37.2	44.6
Smoking during pregnancy (%)	0.7	1.7	7.5
Selected OB/GYN conditions [†] (%)	8.6	7.4	3.1
Plurality at birth (%)			
Singletons	74.0	91.7	98.6
Twins	26.0	8.3	1.4
Length of Gestation (%)			
<32 Weeks	3.7	1.8	1.0
32-36 Weeks	18.0	9.9	5.9
37 Weeks	78.3	88.3	93.1
Method of delivery (%)			
Vaginal	44.6	51.8	66.7
VBAC	1.2	3.0	2.0
Primary Cesarean	40.7	23.8	18.5
Repeat Cesarean	13.5	21.5	12.8

* All differences across the three fertility groups, between ART and SUBFERTILE and between ART and FERTILE were significant at a level of at least $p < 0.01$.

[†] Selected conditions include: endometriosis, polycystic ovarian syndrome, tubal/abdominal/ovarian pregnancy, pelvic inflammatory disease, and peritoneal adhesions.

Table 3
Risk of Severe Maternal Morbidity by Fertility Group Status, Plurality, and Mode of Delivery

Plurality	Reference group	Fertility status	Vaginal Deliveries				Cesarean Deliveries			
			Total in subgroup	% with SMM*	OR (95% CI)	aOR† (95% CI)	Total in subgroup	% with SMM*	OR (95% CI)	aOR† (95% CI)
Singletons	Fertile as ref.	Fertile	297,800	0.59	1.00 (ref)	1.00 (ref)	132,600	2.07	1.00 (ref)	1.00 (ref)
		Subfertile	4,585	0.65	1.11 (0.77, 1.60)	1.16 (0.80, 1.68)	3,442	1.86	0.90 (0.70, 1.15)	0.95 (0.73, 1.23)
		ART	5,492	1.44	2.46 (1.96, 3.09)	2.27 (1.78, 2.88)	4,631	3.37	1.65 (1.40, 1.94)	1.67 (1.40, 1.98)
Twins	Subfertile as ref.	Subfertile	4,585	0.65	1.00 (ref)	1.00 (ref)	3,442	1.86	1.00 (ref)	1.00 (ref)
		ART	5,492	1.44	2.21 (1.46, 3.36)	1.97 (1.30, 3.00)	4,631	3.37	1.84 (1.37, 2.46)	1.75 (1.30, 2.35)
		Fertile	1,928	3.94	1.00 (ref)	1.00 (ref)	4,159	4.26	1.00 (ref)	1.00 (ref)
Twins	Fertile as ref.	Subfertile	209	4.31	1.10 (0.54, 2.22)	1.19 (0.56, 2.55)	518	4.44	1.05 (0.67, 1.63)	1.15 (0.72, 1.84)
		ART	778	4.50	1.15 (0.76, 1.73)	1.24 (0.76, 2.01)	2,776	5.76	1.38 (1.11, 1.71)	1.48 (1.14, 1.93)
		Subfertile	209	4.31	1.00 (ref)	1.00 (ref)	518	4.44	1.00 (ref)	1.00 (ref)
		ART	778	4.50	1.05 (0.49, 2.21)	1.03 (0.48, 2.18)	2,776	5.76	1.32 (0.84, 2.06)	1.27 (0.81, 1.99)

* Unadjusted %.

† Models adjusted for maternal age, education, race/ethnicity, marital status, insurance, parity, smoking during pregnancy, pre-pregnancy hypertension, pre-pregnancy diabetes mellitus, the selected obstetric and gynecologic conditions (endometriosis, polycystic ovarian syndrome, pelvic inflammatory disease, and peritoneal adhesions), and length of gestation.