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Risk of severe maternal morbidity by maternal fertility status: a US study in 8 states

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Abstract

BACKGROUND: Over the past 2 decades the characteristics of women giving birth in the United States and the nature of the births themselves have changed dramatically, with increases in older maternal age, plural births, cesarean deliveries, and conception from infertility treatment.

OBJECTIVE: We sought to evaluate the risk of severe maternal morbidity by maternal fertility status, and for in vitro fertilization pregnancies, by oocyte source and embryo state combinations.

STUDY DESIGN: Women in 8 states who underwent in vitro fertilization cycles resulting in a live birth during 2004 through 2013 were linked to their infant's birth certificates; a 10:1 sample of births from non-in vitro fertilization deliveries were selected for comparison; those with an indication of infertility treatment on the birth certificate were categorized as subfertile, all others were categorized as fertile. In vitro fertilization pregnancies were additionally categorized by oocyte source (autologous vs donor) and embryo state (fresh vs thawed). Maternal morbidity was identified from the birth certificate, modeled using logistic regression, and reported as adjusted odds ratios [95% confidence intervals]. The reference group was fertile women.

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RESULTS: The study population included 1,477,522 pregnancies (1,346,118 fertile, 11,298 subfertile, 80,254 in vitro fertilization autologous-fresh, 21,964 in vitro fertilization autologous-thawed, 13,218 in vitro fertilization donor-fresh, and 4670 in vitro fertilization donor-thawed pregnancies): 1,420,529 singleton, 54,573 twin, and 2420 triplet+ pregnancies. Compared to fertile women, subfertile and the 4 groups of in vitro fertilization–treated women had increased risks for blood transfusion and third- or fourth-degree perineal laceration (subfertile, 1.58 [1.23–2.02] and 2.08 [1.79–2.43]; autologous-fresh, 1.33 [1.14–1.54] and 1.37 [1.26–1.49]; autologous-thawed, 1.94 [1.60–2.36] and 2.10 [1.84–2.40]; donor-fresh, 2.16 [1.69–2.75] and 2.11 [1.66–2.69]; and donor-thawed, 2.01 [1.38–2.92] and 1.28 [0.79–2.08]). Also compared to fertile women, the risk of unplanned hysterectomy was increased for in vitro fertilization–treated women in the autologous-thawed group (2.80 [1.96–4.00]), donor-fresh group (2.14 [1.33–3.44]), and the donor-thawed group (2.46 [1.33–4.54]). The risk of ruptured uterus was increased for in vitro fertilization-treated women in the autologous-fresh group (1.62 [1.14–2.29]). Among women with a prior birth, the risk of blood transfusion after a vaginal birth was increased for subfertile women (2.91 [1.38–6.15]), and women in all 4 in vitro fertilization groups (autologous-fresh, 1.93 [1.23–3.01]; autologous-thawed, 2.99 [1.78–5.02]; donor-fresh, 5.13 [2.39–11.02]; and donor-thawed, 5.20 [1.83–14.82]); the risk after a cesarean delivery was increased in the autologous-thawed group (1.74 [1.29–2.33]) and the donor-fresh group (1.62 [1.07–2.45]). Unplanned hysterectomy was increased in the autologous-thawed (2.31 [1.43–3.71]) and donor-thawed (2.45 [1.06–5.67]) groups.

CONCLUSION: The risks of severe maternal morbidity are increased for subfertile and in vitro fertilization births, particularly in pregnancies that are not from autologous, fresh cycles.

Keywords

autologous-fresh; autologous-thawed; blood transfusion; cesarean delivery; donor-fresh; donor-thawed; embryo state; in vitro fertilization; infertility; oocyte source; perineal laceration; peripartum hysterectomy; severe maternal morbidity; subfertility; twin and triplet births; unplanned hysterectomy

Introduction

Births in the United States from in vitro fertilization (IVF) have doubled from 2000 through 2015, and currently account for 1.8% of all births.[1-4] Although the use of autologous oocytes and fresh embryos has been the norm since IVF treatment began in the 1980s, in recent years there has been a national and international shift in practice to freezeonly, believed to provide better endometrial development than the controlled ovarian stimulation required with autologous-fresh transfers.[5-9] While there is growing evidence from clinical studies that the freeze-only approach is associated with better rates of implantation, clinical pregnancy, ongoing pregnancy, and live birth with thawed vs fresh embryo transfers,[10-12] little is known regarding the consequences at delivery.

Although an estimated 12% of reproductive-aged women and 9.4% of reproductive-aged men have ever used infertility services, IVF represents only a small portion of all infertility treatment used in the United States. Results of the 2006 through 2010 National Survey of Family Growth reported that the most commonly used infertility services among women

ages 25–44 years included medical advice (9.4%), infertility testing (male or female, 7.3%), medical help to prevent miscarriage (6.8%), and ovulation drugs (5.8%). Artificial insemination was reported by 1.7% of women ages 25–44 years (~714,000 women), and surgery for blocked tubes by 1.3% of women (~531,000). Assisted reproductive technology (ART), including IVF, was the least common service ever used, reported by 0.7% of women ages 25–44 years (~275,000 women).[13] Among women with current infertility problems, an estimated 3.1% had ever used ART. The purpose of this analysis is to evaluate the risk of severe maternal morbidity by maternal fertility status, and for IVF pregnancies, by oocyte source and embryo state combinations.

Materials and Methods

This study involved linking data from the national IVF database, the Society for Assisted Reproductive Technology (SART) Clinic Outcome Reporting System (CORS), to birth certificates as part of a larger study in 14 states on ART and risk of childhood cancer (National Institutes of Health grant R01 CA151973). The data for this analysis were limited to live births (≥22 weeks' gestation and ≥300 g birthweight) to mothers at least 18 years of age in study states in which the 2003 revision of the birth certificate had been implemented and its data available (California, Colorado, Florida, Michigan, New York, Ohio, Pennsylvania, and Texas).

SART CORS data

The SART maintains Health Insurance Portability and Accountability Act of 1996–compliant Business Associate Agreements with its 375 reporting clinics. In 2004, following a contract change with the Centers for Disease Control and Prevention, SART leveraged the SART CORS data for the purposes of conducting research. The database includes information on demographic factors, IVF diagnoses and treatment parameters, and pregnancy outcomes. The data in the SART CORS are validated annually with some clinics having on-site visits for chart review. During each visit, data reported by the clinic are compared with information recorded in the medical record; most data fields have discrepancy rates <2%, with diagnosis fields ranging from 2–5%.[14]

Birth certificate data

The 2003 revision of the birth certificate includes specific severe maternal morbidities occurring within 24 hours before or after delivery: maternal transfusion; third- or fourth-degree perineal laceration (vaginal births); ruptured uterus; unplanned hysterectomy; and admission to intensive care. Also in the 2003 revision of the birth certificate, 3 check boxes were added to indicate: (1) the pregnancy resulted from infertility treatment ("if yes, check all that apply"); (2) fertility-enhancing drugs, artificial insemination, or intrauterine insemination; and (3) ART (eg, IVF, gamete intrafallopian transfer). Pregnancies that linked to the SART CORS cycles were categorized as IVF; pregnancies with an indication that they resulted from infertility treatment (via the infertility check box) but did not link to an IVF cycle were categorized as subfertile; the remaining pregnancies were categorized as fertile.

Linkage procedure

In the course of conducting a study on childhood cancer following IVF, we linked the SART CORS data and state vital records. Each state received a file of cycles of women who were residents of that state. To begin the linkage process, a limited data file was generated by Redshift Technologies Inc (New York, NY), the organization that maintains the CORS on behalf of SART, containing only the following factors: study-specific patient identification (ID) and cycle ID; woman's first name, middle name or initial, and last names; Social Security number; date of birth; ZIP code of residence; date of cycle outcome (live birth); plurality of the live birth; and gender(s) and birthweight(s) of the infant(s). The state then performed a linkage to identify the IVF births; 91% of IVF-conceived births in the SART CORS were linked to their respective birth certificates. For each delivery identified as having been conceived by IVF, we requested that the subsequent 10 deliveries (all liveborn infants from a pregnancy) be selected as the non-IVF comparison group, although not all states implemented this request, providing the next 10 births (individual children) instead, and often only 1 infant from a twin or triplet+ pregnancy. The files of the study children were then linked to each state's vital records. Once all data were linked and complete, the files were stripped of all identifying elements (eg, names, dates, Social Security numbers, and any other information that could identify an individual), but retaining the patient ID and cycle ID for the IVF group. The deidentified files were then transmitted to the investigators using secure file transfer methods. For the investigators, Redshift Technologies Inc created a deidentified data file with the study-specific patient ID and cycle ID, and the IVF treatment parameters, and sent the file by secure transfer methods. We then merged the 2 deidentified data files using the patient ID and cycle ID. This study was approved by the institutional review boards at Michigan State University, the University of Michigan, the University of Minnesota, and each of the state departments of health.

The data files received from the states were indexed by infant. However, in this study the analysis was by mother. Although the family structure (siblings) could be reliably determined for the IVF infants, this was not true for the controls, as discussed above. Therefore, each record of a multiple birth was weighted by 1/plurality; ie, if the birth was recorded as a twin, each record would receive the weight of one-half and if a triplet, a weight of one-third. Summing the records in the same family using this weight would then estimate the mother's outcome correctly. (If it was possible to use frequencies instead of weights, both means and SD would be correctly estimated, but software [SAS; SAS Institute Inc, Cary, NC] does not allow frequencies <1.) Weighting reduces the estimate of the SD; therefore, the SD were computed without weights. The means and SD can be interpreted in the usual manner as estimates that apply to an observation.

Comparison groups

Women were classified as IVF-treated only if the state matched the subject to a record in the SART CORS; >90% of the women in SART CORS were identified by the matching. The IVF-treated subjects were then divided into 4 subgroups depending on the source of the oocyte (autologous or donor) and the state of the embryo (fresh or thawed). The control subjects were divided into 2 groups: fertile and subfertile; a woman was assigned to the subfertile group if she responded positively to any of the infertility questions on the birth

certificate. Therefore, 6 maternal fertility status groups were created; the fertile women were treated as the reference group in the modeling.

Variables

Independent variables included maternal age at delivery (continuous and as 18–29, 30–34, 35–37, 38–40, 41–44, and ≥45 years), race (white, black, Asian, other) and Hispanic ethnicity, education (<8th grade, some high school, high school graduate or General Educational Development, some college or associate degree, bachelor degree, or postgraduate education), hypertension (none, chronic, or either gestational or eclampsia), diabetes mellitus (none, chronic, or gestational), parity (nulliparous, 1, or ≥2), mode of delivery (vaginal, cesarean, and repeated cesarean), length of gestation (continuous and as <28, 28–32, 33–36, and ≥37 weeks), and infant sex. IVF treatment parameters included the number of prior IVF cycles, infertility diagnoses (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal factors, uterine factors, other factors, and unexplained), number of embryos transferred (1, 2, >2), and number of fetal heartbeats at 6 weeks' gestation (1, 2, or >2). Dependent variables included the 5 severe morbidity measures as well as hysterectomy after cesarean, which were calculated by maternal fertility status group, overall as well as for women with a prior birth. Perineal laceration was limited to vaginal births only.

Statistical methods

We modeled the risk of each severe morbidity measure and unplanned hysterectomy after vaginal birth and after cesarean birth using logistic regression as adjusted odds ratios (AOR) and 95% confidence intervals controlling for maternal fertility status, age, race and ethnicity, parity, medical conditions (diabetes mellitus and hypertension), plurality at birth, mode of delivery, state of residence, year of birth, and infant sex. For unplanned hysterectomy, we modeled the risk overall and after a vaginal delivery and after a cesarean delivery. We repeated this analysis limited to women with a prior delivery, additionally controlling for prior mode of delivery. For third- or fourth-degree perineal laceration analyses were limited to singleton vaginal births only and the models included length of gestation. Only models with sufficient sample size are presented in the tables. All analyses were performed using software (SAS, Version 9.4).

Results

The study population included 1,477,522 pregnancies (1,346,118 fertile, 11,298 subfertile, 80,254 IVF autologous-fresh, 21,964 IVF autologous-thawed, 13,218 IVF donor-fresh, and 4670 IVF donor-thawed pregnancies): 1,420,529 singleton, 54,573 twin, and 2420 triplet+ pregnancies. A description of maternal characteristics by fertility group and plurality are shown in Table 1. Women in the fertile group were more likely to be younger, Hispanic, and multiparous, and were less likely to be college graduates compared to the subfertile and IVF groups, which for most characteristics tended to be similar.

The infertility diagnoses and IVF treatment parameters are shown in Table 2. Fewer women using fresh embryos had prior IVF cycles, averaging 52.1–61.1% (using autologous oocytes)

and 66.8–71.3% (using donor oocytes). Women using thawed embryos were more likely to have had prior IVF cycles, averaging 91.3–92.9% (using autologous oocytes) and 81.8–89.9% (using donor oocytes). Male factor infertility was the most frequent diagnosis among women using autologous oocytes, regardless of embryo state or plurality, accounting for 40–45% of diagnoses. For women using donor oocytes, diminished ovarian reserve was the most common diagnosis, accounting for 72–79% for diagnoses, regardless of embryo state and plurality. Only 12.2–24.1% of singleton IVF births had a single embryo transferred, 65.3–83.5% of twin births had 2 embryos transferred, and 56.3–79.5% of triplet+ births had >2 embryos transferred, indicating probable evidence of fetal loss and embryo splitting.

The pregnancy, birth, and infant outcomes by fertility group and plurality are shown in Table 3. Subfertile women had the highest rates of gestational diabetes in singleton (9.2%) and twin (10%) births, and any morbidity (2477/100,000 pregnancies) and third- or fourth-degree perineal laceration in singleton and twin births (3477/100,000 pregnancies and 1230/100,000 pregnancies, respectively). Within each fertility group, the rates of third- or fourth-degree perineal laceration were highest among nulliparas (rates for 100,000 pregnancies for fertile, subfertile, and IVF women: nulliparas: 2115, 3990, and 2913, respectively; parity = 1: 593, 1214, and 1075, respectively; and parity ≥2: 229, 273, and 787, respectively) (data not shown). Women with donor-fresh or donor-thawed cycles had the highest rates of pregestational and gestational hypertension within each plurality. Regardless of fertility group, singleton births were more likely to be delivered vaginally, whereas >74% of twins and >93% of triplet+ births were delivered by cesarean. Within each plurality, fertile women were more likely to deliver vaginally.

The results of the logistic regression models of the risks of severe maternal morbidity for the total study population are shown in Table 4, and limited to women with a prior birth in Table 5. Among the total study population, compared to fertile women, the risk of blood transfusion and third- or fourth-degree perineal laceration was increased for subfertile and each of the 4 oocyte source-embryo state IVF groups. The risk of unplanned hysterectomy and hysterectomy after cesarean delivery was increased for the IVF groups with autologous-thawed, donor-fresh, and donor-thawed. Ruptured uterus was elevated for the autologous-fresh IVF group compared to fertile women.

The pattern was similar among women with a prior delivery, with some risks magnified (Table 5). The risk of blood transfusion after vaginal delivery was increased for subfertile and all 4 groups of IVF-treated women; the risk after cesarean was increased for the autologous-thawed and donor-fresh groups. The risk of unplanned hysterectomy was increased for pregnancies from autologous-thawed and donor-thawed cycles.

Comment

Main findings

Defined as unexpected outcomes of labor and delivery that result in significant short- or long-term consequences to a woman's health, severe maternal morbidity affects an estimated 52,000 women annually in the United States.[15,16] These analyses demonstrate that the risks of severe maternal morbidity are increased for subfertile and IVF-treated

women, particularly in pregnancies that are not from autologous, fresh cycles. These data suggest that adverse maternal outcomes associated with IVF may be at least in part due to underlying infertility.

In analyses adjusted for potential confounders, the risks of unplanned hysterectomy were highest among pregnancies achieved with thawed embryos (AORs of 2.76 for autologous oocytes and 2.05 for donor oocytes for the total population [Table 4], and 2.31 for autologous oocytes and 2.45 for donor oocytes for parous women [Table 5]).

Clinical implications

In IVF cycles without ovarian hyperstimulation, such as frozen or donor cycles, there is a lower risk of ectopic pregnancy, suggesting that factors influencing the tubal-uterine environment may influence abnormal implantation.[17-19] Unlike autologous-fresh cycles, neither thawed embryo cycles nor donor oocyte involve ovarian hyperstimulation in the recipient woman. Londra et al[19] hypothesize that ovarian hyperstimulation results in a uterine environment that increases the risk of endometrial implantation failure and an abnormally located implantation compared with embryo transfer without ovarian hyperstimulation. While clinical studies have reported better rates of implantation, clinical pregnancy, ongoing pregnancy, and live birth with frozen vs fresh embryo transfers,[11,18,20] these cycles have consistently been associated with increased risks for placenta accreta and pregnancy-induced hypertension,[12,22] as well as an excess of large-for-gestation birthweights.[21-23] Although our study does not have data on abnormal placentation, the risk of blood transfusion was increased for the subfertile group and all 4 IVF groups in analyses based on the total population (Table 4), and in vaginal births among parous women (Table 5). The risk of unplanned hysterectomy was increased in autologous-thawed and donor-fresh and donor-thawed groups in the total population (Table 4), and after cesarean birth in autologous-thawed and donor-thawed groups among parous women (Table 5).

A consistent finding in IVF- and ART-conceived pregnancies is an increased risk of uterine bleeding and placental complications, regardless of plurality, and a greater risk for blood transfusions.[24-29] Our results confirm the higher risk of blood transfusions in both subfertile and IVF-conceived pregnancies, and greater likelihood of unplanned hysterectomy in IVF-conceived births, particularly in pregnancies that are not from autologous, fresh cycles. In their analysis of all births in Norway in 1999 through 2009, Ebbing et al[27] reported increased risks for velamentous and marginal cord insertions with ART (2-fold for singletons, and 4-fold for twins), and a 20–80% risk of recurrence. The subfertility group in our study, although similar to the IVF group in demographic characteristics, generally showed higher rates of severe maternal morbidity, more consistently in twin and triplet+ births. Unlike IVF cycles, identifying non-IVF ART treatments is challenging, as there is no national registry for these treatments. These women may have received IVF treatment from clinics that did not report to either SART (about 17% of all clinics and 9% of all IVF cycles) or the Centers for Disease Control and Prevention (35 out of 499 clinics in 2015), representing less standardized therapy. They may differ in other ways that were not measured in this study, including socioeconomic, anthropometric, and financial factors.

Higher plurality, which is more frequent in subfertile and IVF pregnancies, is a well-established factor for adverse perinatal outcomes, including greater risks for severe maternal morbidity.[30-33] These risks may be related to over-distention of the uterus due to greater fetal number, as well as factors associated with altered placentation in IVF and ART conceptions. Our prior analyses of twin pregnancies (which were additionally linked to hospital discharge data, as well as birth certificates) have reported a 2-fold increased risk of uterine bleeding and placental complications (abruptio placenta, placenta previa, vasa previa) in subfertile and IVF pregnancies.[34]

Nationally in the United States, cesarean rates parallel advancing maternal age: in 2015, women aged ≥40 years were more than twice as likely to deliver by cesarean as women age <20 years (48.4% vs 20.4%).[1] In 2015, the overall low-risk cesarean delivery rate (cesarean delivery among nulliparous women with full-term singletons in a vertex presentation) was 25.8%, ranging from 16.7% for women ages <20 years to 52.0% for women ages ≥40 years.[1] The use of forceps, vacuum extraction, and vaginal births after cesarean has declined dramatically in recent years.[35,36] The rise in cesarean births has paralleled the rate of peripartum hysterectomy, an indicator of severe postpartum hemorrhage.[37] An analysis of the 1994 through 2007 Nationwide Inpatient Sample showed a 15% overall increase in peripartum hysterectomy, including a 23% increase due to abnormal placentation and a 130% increase due to uterine atony (primarily associated with cesarean delivery).[37] During this time period, the rate of severe postpartum hemorrhage (with transfusion or hysterectomy) has doubled.[38,39] Abnormal placentation (placenta accreta, vasa previa, placenta previa, abruptio placenta, and retained placenta) and postpartum hemorrhage from uterine atony are the leading indicators for peripartum hysterectomy.

Strengths and weaknesses

A common problem in observational studies is unmeasured confounders. As can be seen in Table 1, subjects who underwent infertility treatment (subfertile or IVF) were more likely to be white, non-Hispanic, more educated, and older than the fertile controls. These differences may be indicative of unmeasured confounders, such as income, medical insurance, and prenatal care, which may affect maternal morbidity. Although race, ethnicity, education, and age were included in the logistic models, it is not possible to estimate the effect of the unmeasured confounders on the AORs.

The states reported matches for >90% of the records in the SART CORS database to women who delivered. Mis-identifications by the states would have the effect of including non-IVF subjects in the IVF groups; this would reduce the AORs of the IVF groups. Luke et al[40] showed that there is a large under-reporting of the use of infertility treatment on the birth certificate. Women who did not report their infertility treatment would be included in the fertile group; this would reduce the AOR of the subfertile group (and of the IVF groups). Therefore, the result of misclassification is to reduce the AORs.

Known limitations of birth certificate data include the unreliability of selected items (eg, maternal weight gain) and the high rate of missing values for other items (eg, father's age and race/ethnicity, maternal height and prepregnancy weight).[1] The validity of birth certificate data using the medical record as the gold standard has been assessed, with most

items reported accurately, with high specificity and wide variance in sensitivity, reflecting that if a rare condition was present, it often was not documented, but if the condition was documented, it was likely that it was present.[41,42]

A major strength of this study is that the SART CORS data were collected prior to and separately from the vital statistics data, so we expect no differential misclassification of maternal morbidity with respect to IVF. These findings are subject to several limitations. The low frequency of ruptured uterus has been previously documented in studies evaluating hospital discharge data[43] and the severe morbidity measures on the birth certificate, suggesting difficulty in distinguishing between the diagnoses of a ruptured uterus and uterine dehiscence.[44] A recent comparison of the severe maternal morbidity measures on the birth certificate with *International Classification of Diseases, Ninth Revision* coding in delivery admission hospital discharge data showed that the former are greatly underreported, with sensitivities ranging from 0.11 (blood transfusion in vaginal births) to 0.52 (unplanned hysterectomy after cesarean delivery), and positive predictive values ranging from 0.03–0.90, with highest values for blood transfusion and perineal lacerations.[45]

Conclusion and future research direction

These analyses demonstrate that the risks of severe maternal morbidity are increased for subfertile and IVF-treated women, particularly in pregnancies that are not from autologous, fresh cycles. The findings of >2-fold increased risk of unplanned hysterectomy in thawed IVF cycles warrant further study, particularly given the increasing utilization of frozen embryo transfer including freeze-only cycles. As the characteristics of the childbearing population continue to change, it is important that severe maternal morbidity be monitored and validated on a national basis. ■

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AJOG at a Glance

Why was this study conducted?

To evaluate the risks of severe maternal morbidity by maternal fertility status and plurality.

Key findings

Among the total study population, the risk of blood transfusion was increased for the subfertile group and the 4 in vitro fertilization groups; the risk of unplanned hysterectomy was increased for autologous-thawed, donor-fresh, and donor-thawed groups. Risk of ruptured uterus was increased for the autologous-fresh group.

What does this add to what is known?

The risks of severe maternal morbidity are increased for subfertile and in vitro fertilization–treated women, particularly in pregnancies that are not from autologous, fresh cycles.

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TABLE 1

Maternal characteristics by fertility group and plurality

	Singletons						Twins						Triplets+[a]					
			IVF						IVF						IVF			
	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed
N, pregnancies	1,326,650	9142	56,037	16,997	8129	3574	19,116	1951	22,858	4686	4921	1041	352	205	1359	281	168	55
Maternal age, y																		
Mean (SD)	28.7 (5.9)	33.7 (5.2)	35.0 (4.3)	35.0 (4.3)	42.1 (4.7)	42.9 (5.1)	29.7 (5.8)	34.5 (5.4)	33.9 (4.0)	34.2 (4.1)	41.8 (4.8)	42.4 (5.2)	31.2 (5.6)	32.9 (5.2)	33.8 (3.9)	33.8 (4.2)	40.8 (4.7)	42.9 (5.2)
%																		
18–29	55.3	21.0	10.5	9.9	1.3	1.7	48.1	16.4	14.5	12.0	1.7	2.1	36.8	24.8	15.0	17.5	1.2	0.0
30–34	26.9	36.0	34.0	35.1	6.2	5.8	30.1	37.5	40.7	41.6	7.0	6.9	36.7	43.4	39.4	39.4	8.0	5.5
35–37	10.3	19.6	24.9	26.4	7.5	7.1	12.5	21.2	25.0	25.0	8.9	8.2	14.2	13.8	26.5	24.0	14.3	12.7
38–40	5.3	13.8	20.1	18.7	15.4	12.3	6.6	12.6	15.3	15.0	15.8	14.0	8.1	10.0	15.3	13.7	19.4	10.9
≥41	2.1	9.5	10.5	9.9	69.6	73.2	2.7	12.3	4.4	6.4	66.7	68.9	4.2	8.0	3.8	5.5	57.1	70.9
Hispanic ethnicity, %	26.4	7.3	8.6	9.4	8.0	9.4	20.7	6.8	11.1	13.3	8.2	6.7	18.8	9.9	4.8	5.3	4.5	5.2
Race, %																		
White	76.7	86.7	81.7	78.3	83.7	83.7	75.2	85.7	83.9	78.3	83.9	84.3	79.0	91.4	86.3	77.8	84.8	84.6
Black	13.2	4.0	4.8	5.3	4.5	5.2	17.4	4.1	4.4	6.1	5.3	4.9	15.0	3.3	5.3	9.2	6.6	11.5
Asian	9.5	8.9	13.2	16.1	11.5	10.9	7.0	10.0	11.5	15.4	10.5	10.6	5.2	4.6	8.4	12.6	7.9	3.8
Other	0.5	0.3	0.2	0.3	0.2	0.3	0.4	0.2	0.2	0.2	0.3	0.2	0.7	0.7	0.0	0.4	0.6	0.0
Education, %																		
<8th Grade	4.7	0.3	0.3	0.6	0.4	0.3	3.6	0.3	0.3	0.3	0.4	1.2	1.8	0.0	0.2	2.6	1.2	0.0
Some high school	12.1	1.5	1.0	1.2	0.9	0.8	10.3	1.3	1.0	1.0	0.8	0.8	6.7	1.6	1.4	2.1	0.0	0.0
High school graduate or GED	24.4	8.3	7.1	7.7	6.8	6.1	23.1	8.1	7.7	7.6	7.1	6.4	21.1	11.0	12.1	9.9	10.7	12.3

	Singletons						Twins						Triplets+[a]					
			IVF						IVF						IVF			
	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed	Fertile	Subfertile	A-fresh	A-thawed	D-fresh	D-thawed
Some college or associate degree	27.0	20.9	18.5	18.1	16.3	18.6	27.2	17.8	19.6	19.2	17.2	20.5	27.2	28.1	23.1	26.6	24.1	20.4
Bachelor's degree	20.3	37.5	39.8	38.8	39.6	38.7	22.1	37.0	40.4	38.7	39.5	37.0	25.6	29.8	35.3	35.2	36.7	52.5
Postgraduate	11.6	31.6	33.3	33.6	36.1	35.4	13.6	35.5	31.0	33.1	34.9	34.1	17.6	29.5	27.9	23.7	27.2	14.8
Parity, %																		
Nulliparous	38.7	56.4	70.0	51.9	69.9	50.9	20.2	29.7	40.4	32.2	39.3	29.7	16.1	16.9	26.8	21.6	25.3	17.4
1	33.0	29.9	22.4	34.1	21.7	35.7	35.4	42.0	43.6	42.5	43.1	41.0	26.0	28.0	29.4	27.8	29.6	25.9
≥2	28.2	13.6	7.6	14.0	8.4	13.4	44.5	28.3	16.0	25.3	17.6	29.2	57.9	55.1	43.8	50.6	45.1	56.7

Missing: age 0.012%, race 5.8%, parity 20%, education 1.5%; length of gestation 0.9%.

Means are weighted; SDs are not weighted.

GED, General Educational Development; *IVF*, in vitro fertilization.

[a]Includes triplets, quadruplets, quintuplets, and sextuplets.

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TABLE 2

Infertility diagnoses and in vitro fertilization treatment parameters by plurality

Plurality at birth	**Singletons**				**Twins**				**Triplets+**			
Oocyte source-embryo state	**Autologous-fresh**	**Autologous-thawed**	**Donor-fresh**	**Donor-thawed**	**Autologous-fresh**	**Autologous-thawed**	**Donor-fresh**	**Donor-thawed**	**Autologous-fresh**	**Autologous-thawed**	**Donor-fresh**	**Donor-thawed**
N, pregnancies	56,037	16,997	8129	3574	22,858	4686	4921	1041	1359	281	168	55
Prior IVF												
Women with prior cycles, %	54.3	91.7	66.8	89.9	52.1	91.3	68.1	87.2	61.1	92.9	71.3	81.8
Prior cycles, mean (SD)	1.6 (2.2)	2.7 (2.6)	2.5 (2.9)	3.7 (3.5)	1.5 (2.1)	2.4 (2.2)	2.6 (2.9)	3.3 (3.1)	1.8 (2.2)	2.7 (2.3)	2.6 (3.1)	3.4 (3.3)
Diagnoses male factor, %	40.5	40.0	19.7	19.9	42.2	40.1	21.0	19.9	45.3	42.4	29.1	20.0
Endometriosis	12.0	11.7	6.6	6.9	12.9	11.9	6.6	7.4	13.6	13.9	7.2	1.8
Ovulation disorders	15.8	20.1	3.2	4.4	18.2	21.7	4.4	4.5	18.1	24.3	3.2	5.5
Diminished ovarian reserve	16.3	10.6	78.2	77.4	11.2	8.2	77.9	75.8	11.8	6.4	72.5	79.4
Tubal factors	16.1	16.7	6.9	7.8	16.7	17.6	7.6	8.2	19.4	24.3	11.1	9.7
Uterine factors	4.3	4.5	4.8	5.7	3.9	4.1	4.7	5.4	3.8	3.1	3.8	3.6
Other factors	11.8	12.2	16.4	16.6	10.7	11.6	15.5	17.3	10.0	9.6	10.0	12.7
Unexplained	13.7	13.0	3.6	2.9	13.8	13.1	3.6	3.5	12.5	8.6	5.4	1.8
Embryos transferred, %												
1	12.2	24.1	15.3	21.8	0.6	1.9	0.3	1.4	0.3	0.7	0.0	0.0
2	53.1	51.0	70.8	53.4	65.3	63.1	83.5	63.8	26.8	19.8	43.7	14.5
>2	34.8	24.9	14.0	24.8	34.1	35.0	16.1	34.7	73.0	79.5	56.3	85.5
Fetal heartbeats at 6 wk, %												
1	92.0	94.3	89.2	94.1	0.9	1.0	0.5	1.5	0.4	1.3	1.8	0.0
2	7.1	5.2	9.5	5.4	93.5	93.5	95.4	93.6	4.4	1.4	4.6	4.8
>2	0.9	0.5	1.2	0.6	5.6	5.5	4.1	4.9	95.1	97.2	93.6	95.2

IVF, in vitro fertilization.

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TABLE 3

cy, birth, and infant outcomes by maternal fertility group and plurality at birth

	Singletons						Twins						Triplets+					
			IVF						IVF						IVF			
	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed
es	1,326,650	91	56,037	16,997	8129	3574	19,116	1951	22,858	4686	4921	1041	352	205	1359	281	168	55
%																		
onal	0.6	0.5	0.7	0.7	0.8	1.0	0.8	1.0	0.6	0.7	0.7	1.1	0.6	1.0	1.5	0.7	3.0	0.0
al	4.4	9.2	6.3	6.5	7.6	8.4	5.7	10.0	7.7	8.4	9.5	9.5	8.3	14.5	9.9	9.6	9.2	12.1
ion,																		
onal ion	1.1	2.2	1.4	1.6	2.8	2.6	1.7	2.5	1.3	1.8	3.1	3.5	1.6	1.9	2.0	2.0	3.2	8.5
al ion	3.5	6.5	4.2	5.0	8.6	7.4	7.7	11.1	8.8	12.3	18.4	15.4	9.4	16.9	13.4	18.3	29.4	19.9
osia	0.2	0.3	0.3	0.2	0.6	0.4	0.6	0.9	0.6	0.6	1.2	0.5	1.2	0.8	0.9	1.2	2.5	0.0
%																		
	67.6	56	54.6	46.3	32.5	31.6	25.2	21.8	18.0	16.2	10.8	12.5	6.9	3.8	4.4	5.9	3.2	1.8
	32.4	43	45.4	53.7	67.5	68.4	74.8	78.2	82.0	83.8	89.2	87.5	93.1	96.2	95.6	94.1	96.8	98.2
	42.4	30	21.4	34.1	16.8	36.3	22.4	17.6	12.5	20.3	12.9	26.7	20.2	18.1	12.4	16.8	13.5	24.2
	38.7 (2.0)	38.4 (2.3)	38.4 (2.2)	38.5 (2.2)	38.2 (2.4)	38.0 (2.4)	35.3 (3.1)	34.9 (3.6)	35.3 (3.0)	35.3 (3.0)	35.3 (2.9)	35.2 (2.9)	31.8 (3.3)	31.8 (3.1)	32.1 (3.2)	32.0 (3.4)	32.1 (2.9)	32.4 (3.2)
%	0.5	1.1	0.7	0.7	0.8	0.8	3.5	5.9	3.3	3.0	2.3	3.0	10.6	10.4	9.8	11.6	7.2	5.6
, %	1.1	1.5	1.7	1.5	2.3	2.8	10.1	12.2	10.4	10.8	11.4	11.5	41.9	40.4	39.1	35.9	44.6	41.4
, %	6.6	8.6	9.0	8.8	12.1	13.3	44.2	41.5	45.0	45.4	48.0	49.8	45.8	47.9	47.7	50.1	44.0	45.7
%	91.9	88.9	88.5	89.0	84.8	83.1	42.2	40.4	41.3	40.8	38.3	35.7	1.8	1.3	3.3	2.4	4.2	7.4

	Singletons						Twins						Triplets+					
			IVF						IVF						IVF			
	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed	Fertile	Subfertile	Autologous-fresh	Autologous-thawed	Donor-fresh	Donor-thawed
	6.0	9.3	7.9	8.4	10.4	10.6	31.4	36.4	32.7	31.7	35.6	36.9	73.4	81.1	79.4	75.8	78.5	75.6
	0.2	0.6	0.2	0.3	0.2	0.3	1.3	2.8	1.0	0.9	0.7	1.0	3.9	2.4	2.9	2.6	0.8	1.2
th	0.4	0.6	0.3	0.4	0.3	0.4	1.8	3.1	1.4	1.2	1.1	1.1	4.3	3.2	3.7	3.1	1.4	4.2
a																		
	1179	2477	1875	2141	1993	1427	1297	1863	1251	2017	2205	2210	2812	3152	2011	4513	2786	5455
n to care	125	135	182	200	381	420	393	373	335	683	904	721	1433	1778	883	2138	1791	0
n	207	405	312	424	590	559	745	1251	709	1206	1433	1201	1470	1890	1251	2850	1791	5455
	31	58	66	65	12	28	73	80	68	43	51	0	0	0	25	238	398	0
d my	33	46	55	159	185	280	122	213	77	277	335	432	92	0	147	356	597	0
gree	1231	342	2506	3205	3254	1596	620	1230	*c*	*c*	*c*	*c*	*c*	*c*	*c*	*c*	*c*	*c*
b																		

o fertilization; *NICU,* neonatal intensive care unit.

0 pregnancies

rths only

t data.

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TABLE 4

Risks of severe maternal morbidity by maternal fertility status

	Intensive care		Blood transfusion		Ruptured uterus		Unplanned hysterectomy		Hysterectomy after cesarean		Third- or fourth-degree perineal laceration[a]	
N, Pregnancies	1,477,522		1,477,522		1,477,522		1,477,522		522,691		942,742	
Outcomes, %	2130	0.14%	3608	0.24%	506	0.03%	611	0.04%	493	0.09%	12,327	1.31%
	AOR	**95% CI**	**AOR**	**95% CI**	**AOR**	**95% CI**	**AOR**	**95% CI**	**AOR**	**95% CI**	**AOR**	**95% CI**
Fertile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Subfertile	0.87	0.58–1.31	1.58[b]	1.23–2.02[b]	1.47	0.67–3.23	1.08	0.55–2.11	0.91	0.43–1.96	2.08[b]	1.79–2.43[b]
IVF autologous-fresh	0.88	0.74–1.06	1.33[b]	1.14–1.54[b]	1.62[b]	1.14–2.29[b]	1.04	0.74–1.48	0.86	0.58–1.28	1.37[b]	1.26–1,49[b]
IVF autologous-thawed	1.22	0.95–1.57	1.94[b]	1.60–2.36[b]	1.39	0.80–2.45	2.80[b]	1.96–4.00[b]	2.76[b]	1.88–4.04[b]	2.10[b]	1.84–2.40[b]
IVF donor-fresh	1.13	0.84–1.52	2.16[b]	1.69–2.75[b]	0.60	0.20–1.78	2.14[b]	1.33–3.44[b]	1.75[b]	1.02–3.01[b]	2.11[b]	1.66–2.69[b]
IVF donor-thawed	1.08	0.67–1.72	2.01[b]	1.38–2.92[b]	0.33	0.04–2.50	2.46[b]	1.33–4.54[b]	2.05[b]	1.03–4.09[b]	1.28	0.79–2.08

Models adjusted for maternal fertility status, age, parity, race and ethnicity, hypertension and diabetes (pregestational and gestational), plurality at birth, length of gestation, and mode of delivery, as well as state and year of birth and infant sex.

AOR, adjusted odds ratio; *CI*, confidence interval; *IVF*, in vitro fertilization.

[a]Limited to singleton vaginal births only, adjusted for all factors in original model, as well as length of gestation

[b]Significantly increased compared to reference group.

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TABLE 5

Risks of severe maternal morbidity among women with prior birth by maternal fertility

	Admission to intensive care		Blood transfusion				Unplanned hysterectomy	
Mode of delivery	**Cesarean**		**Vaginal**		**Cesarean**		**Cesarean**	
N, Pregnancies	250,345		452,953		250,345		250,345	
Outcomes, %	720	0.29%	451	0.10%	937	0.37%	286	0.11%
	AOR	**95% CI**	**AOR**	**95% CI**	**AOR**	**95% CI**	**AOR**	**95% CI**
Fertile	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Subfertile	0.58	0.25–1.35	2.91[a]	1.38–6.15[a]	1.04	0.58–1.84	0.85	0.27–2.71
IVF autologous-fresh	0.84	0.62–1.15	1.93[a]	1.23–3.01[a]	1.06	0.82–1.37	0.79	0.48–1.33
IVF autologous-thawed	1.37	0.94–1.99	2.99[a]	1.78–5.02[a]	1.74[a]	1.29–2.33[a]	2.31[a]	1.43–3.71[a]
IVF donor-fresh	1.24	0.78–1.97	5.13[a]	2.39–11.02[a]	1.62[a]	1.07–2.45[a]	1.38	0.62–3.06
IVF donor-thawed	0.84	0.39–1.82	5.20[a]	1.83–14.82[a]	1.64	0.94–2.87	2.45[a]	1.06–5.67[a]

Models adjusted for maternal fertility status, age, parity, race and ethnicity, hypertension and diabetes (pregestational and gestational), plurality at birth, length of gestation, mode of delivery, and prior mode of delivery, as well as state and year of birth and infant sex.

AOR, adjusted odds ratio; *CI*, confidence interval; *IVF*, in vitro fertilization.

[a]Significantly increased compared to reference group.

Luke et al. Risk of severe maternal morbidity. Am J Obstet Gynecol 2019.