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ADVERSE PREGNANCY AND BIRTH OUTCOMES ASSOCIATED WITH UNDERLYING DIAGNOSIS WITH AND WITHOUT ART TREATMENT

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Abstract

Objective—To compare the risks for adverse pregnancy and birth outcomes by diagnoses with and without ART treatment to non-ART pregnancies in fertile women.

Design—Historical cohort

Setting—Massachusetts vital records linked to ART clinic data from SART CORS

Patients—Diagnoses included male factor (ART only), endometriosis, ovulation disorders, tubal (ART only) and reproductive inflammatory disorders (non-ART only). Pregnancies resulting in singleton and twin live births from 2004–08 were linked to hospital discharges in women who had ART treatment (N=3,689), women with no ART treatment in the current pregnancy (N=4,098) and non-ART pregnancies to fertile women (N= 297,987).

Interventions—None

Main Outcome Measures—Risks of gestational diabetes, prenatal hospitalizations, prematurity, low birth weight, and small-for-gestation were modeled using multivariate logistic regression with fertile deliveries as the reference group adjusted for maternal age, race/ethnicity, education, chronic hypertension, diabetes mellitus, and plurality (adjusted odds ratios, AORs, and 95% confidence intervals, CI).

Results—Risk of prenatal hospital admissions was increased for endometriosis (ART 1.97, 1.38–2.80; non-ART 3.34, 2.59–4.31), ovulation disorders (ART 2.31, 1.81–2.96; non-ART 2.56, 2.05–3.21), tubal (ART 1.51, 1.14–2.01), and reproductive inflammation (non-ART 2.79, 2.47–3.15). Gestational diabetes was increased for women with ovulation disorders (ART 2.17, 1.72–2.73; non-ART 1.94, 1.52–2.48). Preterm delivery (AORs 1.24–1.93) and low birthweight (AORs 1.27–1.60) were increased in all groups except endometriosis with ART.

Conclusions—The findings indicate substantial excess perinatal morbidities associated with underlying infertility-related diagnoses in both ART-treated and non-ART-treated women.

Keywords

ART; endometriosis; ovulatory disorder; pregnancy outcome; preterm delivery; low birthweight

Introduction

Assisted reproductive technology (ART) has been used to assist couples have children for more than 3 decades. In recent years, evidence has emerged that ART pregnancies are at an increased risk of adverse outcomes. Demonstrated risks have included increased rates of prematurity and low birthweight as well as an increase in infants born small for gestational age (1–3). ART assisted pregnancies have been shown to have increased risk of preeclampsia, gestational diabetes, and bleeding disorders (4–6). Much of the increased risk with ART results from multiple gestation (7), however, risks are increased even in singleton pregnancies (2).

The reasons for the increase in adverse outcomes with ART are not known. One hypothesis is that they result from the ART procedure itself and are caused by medications used to stimulate multiple ovulations, manipulations of gametes, in vitro culture, transfer of multiple embryos, or other treatment related phenomena. Another strong possibility is that underlying infertility-related diagnoses of the women who undergo ART contribute directly to the adverse outcomes. Distinguishing between these possibilities is complicated by the fact that many studies compare ART pregnancies to those of fertile women rather than to those of infertile women who did not undergo ART.

We addressed the question of whether adverse ART outcomes arise from ART treatment or underlying infertility-related diagnoses using data from the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) that uses linked data from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database and the Pregnancy to Early Life Longitudinal (PELL) data system, a vital statistics data system. The goal of this study was to compare the risks for adverse pregnancy and birth outcomes by infertility-related diagnoses with and without ART treatment to pregnancies in a fertile population.

Methods

Study design and setting

This historical cohort study included 305,774 pregnancies resulting in singleton and twin live birth deliveries that took place between July 1, 2004 and Dec 31, 2008 in Massachusetts. To identify ART pregnancies, ART cycles from the SART CORS were linked to Massachusetts vital records in the PELL data system.

Data Sources

The Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS)—The SART CORS database is used by SART to collect national ART data under the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493) and to report these data to the CDC. SART CORS data includes patient demographic information, cycle specific treatment data and outcome data. Data are validated annually through review by SART and CDC.

The Pregnancy to Early Life Longitudinal (PELL) data system—Birth certificate data and hospital discharge data were obtained from the PELL data system. The PELL database was developed as a collaborative effort between the Massachusetts Department of Public Health, the Centers for Disease Control and Prevention (CDC) and Boston University School of Public Health and links vital records from birth and fetal death certificates, hospital discharges, and program data from child health and development programs.

Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART)—The Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) is a project developed to link data from the SART CORS to PELL with the goal of evaluating pregnancy, child health, and women's health outcomes on a population basis. Prior to performing the linkage, a Memorandum of Understanding was executed between SART and the three entities that participate in the PELL project. Human subjects approval was obtained from all entities and participating Universities. The study had the approval of the SART Research Committee.

Participants

Pregnancies resulting in live birth deliveries between July 1, 2004 and December 31, 2008 to women and men older than age 18 were classified as ART if the birth certificate linked to a SART CORS outcome using mother's first and last name, mother's date of birth, father's name, race of both parents, date of delivery, and number of babies born per delivery. Methods for linkage have been described previously (8) and resulted in a linkage rate of 89.7% overall and 95.0% for deliveries in which both ART cycle patient zip code and treatment clinic were located in MA. The linkage yielded deliveries identified for this study as ART deliveries. The linkage identifies live births and fetal deaths but could not identify early pregnancies within the PELL data system. The fetal deaths were not included as they represented less than 1% of deliveries and suppression rules required for use of vital records data in MA would have prevented us from distinguishing the fetal deaths from the live births in the dataset.

Diagnosis groups for ART-treated deliveries were identified through the diagnosis fields reported to the SART CORS and included male factor (N=1,901), endometriosis (N=406), ovulatory disorders (N=676), and tubal disease (706). Of those with tubal disease, 7% had tubal ligation, 7% had hydrosalpinx and the rest had other forms of tubal disease. Diagnosis groups for women who did not undergo ART were identified from Massachusetts deliveries. Women whose deliveries were not linked to SART CORS were included in the non-ART group if they had one or more hospital encounters (admissions, observational stays, or ER visits) of endometriosis (ICD-9 codes 617.0, 617.1, 617.2, 617.3, 617.9; N=590), ovulatory disorders (ICD-9 codes 256.1, 256.39, 256.4, 256.8, 256.9, 626.4, 626.8; N=833), or reproductive inflammation, a category in which we included both reproductive tract (uterus, fallopian tube, ovary) and pelvic inflammatory conditions (ICD-9 codes 614.0, 614.1, 614.2, 614.3, 614.4, 614.5, 614.8, 614.9; N=2,675). Patients were included in one of the above ART-treated and non-ART treated groups if they had a single diagnosis only: patients with multiple infertility-related diagnoses were excluded.

Deliveries to fertile women (N=297,987) were identified as not being in either of the two above groups and not having been included in a previously defined subfertile group (9).

All groups were limited to singleton and twin deliveries of 20 weeks gestation with birthweights between 350 grams and 8,165 grams to mothers age 18 or older with a single diagnosis.

Variables

The pregnancy and birth outcomes analyzed included maternal morbidity (pregnancy hypertension, gestational diabetes), prenatal hospital utilization (emergency room visits, observational stays, and hospital admissions), delivery complication (primary cesarean delivery), and birth outcomes (preterm birth, low birthweight, and small-for-gestational age). The reference group was deliveries to fertile women.

Demographics and underlying conditions—Maternal and paternal demographic characteristics of age, race and ethnicity, and education were obtained from the birth certificate in PELL. Preexisting maternal conditions (diabetes mellitus and chronic hypertension) were determined either from the birth certificates or hospital discharges (ICD9-codes of 648.0 or 250 for diabetes mellitus; 401, 402, 403, 404, or 405 for chronic hypertension).

Maternal health during pregnancy—Uterine bleeding, abruptio placenta, excess bleeding in labor, placenta previa, breech and malpresentation, cephalopelvic disproportion, and mode of delivery were obtained from the birth certificates. Pregnancy hypertension, and gestational diabetes were identified in PELL from either the birth certificate or the hospital discharge delivery record (ICD-9 codes of 642 for pregnancy-related hypertension; 648.8 for gestational diabetes). Prenatal hospitalization was identified in PELL from maternal longitudinal hospital utilization data and categorized as emergency room visits, observational stays, or hospital admissions.

Prematurity and Low Birthweight—Length of gestation was calculated according to an algorithm combining information from the clinical estimate (estimated from early ultrasound) and calculated delivery date (delivery date minus date of last menstrual period). Deliveries were classified as premature if length of gestation was <37 weeks gestation.

Birthweight was obtained from the birth certificates. Low birthweight was characterized as a weight under 2,500 grams.

Birthweight Z-Score—A standard deviation score for birthweights (birthweight z-score) was calculated as the standard deviation score of the value for each individual from the mean value of the reference population divided by the standard deviation for the reference population (10). The birthweight z-score evaluates the adequacy of weight-for-age using population-based standards as recommended by Land (11) and these are modeled as continuous and categorical variables. We generated gender-, race/ethnicity-, and gestation-specific birthweight means and standard deviations using Massachusetts data for all live births from 1998–2008. Any live-born infant with z-scores below the 10th percentile (-1.28 SD) was considered small-for-gestational age.

Statistical Methods

Differences in mean values across groups were analyzed by Student's t-test for two groups, for more than two groups analysis of variance (ANOVA) was used for continuous variables and chi squared for categorical variables with $P < 0.05$ considered statistically significant. We modeled the risks for adverse outcomes with multivariate logistic regression using pregnancies resulting in deliveries to fertile women as the reference group. Models required that all covariates be present and were adjusted for maternal age, race and ethnicity, education, chronic hypertension, pre-pregnancy diabetes mellitus, and plurality, and were reported as adjusted odds ratios (AORs) and 95% confidence intervals (CI). The data were analyzed using SAS software version 9.3 (SAS Institute Inc., Cary, NC, U.S.A) and models computed using general estimating equations (GEE) to account for clustering of outcomes within a mother.

Results

The study population included live birth deliveries to 3,689 women with ART treatment and the single diagnoses of male factor, endometriosis, ovulation disorders, or tubal disease; 4,098 women with no ART treatment and the single diagnosis of endometriosis, ovulation disorders, or reproductive inflammation; and 297,987 women with neither ART treatment nor any of the above diagnoses.

Overall, women with ART treatment (34.5 ± 4.0) were significantly older than either the non-ART treated women with infertility-related diagnoses (26.3 ± 5.6) or the fertile women (29.7 ± 5.8 ; $P < 0.0001$). A higher proportion of mothers and fathers were white in the ART treated groups than in the other groups (84.6%, 85.5% ART; 56.3%, 43.8 non-ART with infertility-related diagnoses; 68.0%, 63.8% fertile for mothers and fathers respectively; $P < 0.0001$). Chronic hypertension and chronic diabetes mellitus differed between the groups (hypertension 3.1% ART, 2.0% non-ART, 1.6% fertile; chronic diabetes 2.3% ART, 2.0%

non-ART, 1.1% fertile; $P<0.0001$). Table 1 shows the distribution of maternal and paternal demographic characteristics and chronic conditions in each diagnosis and treatment category.

There were more twin pregnancies in the ART group (26.4% ART; 1.7% non-ART with infertility diagnoses; 1.4% fertile: $P<0.0001$) and this proportion differed by diagnosis (Table 2). Unadjusted percentages of adverse pregnancy and delivery outcomes also differed. Table 3 presents the AORs for adverse outcomes in each diagnosis group with and without ART treatment. Many groups had higher rates of Cesarean delivery than those to fertile women. Patients with ovulation disorders, endometriosis, tubal disease, and reproductive inflammation had higher rates of hospital admission and all except those with endometriosis and ART had more preterm birth and low birthweight babies. Patients with inflammation also had higher rates of small for gestational age babies.

Discussion

Analysis of pregnancy outcomes for ART treatment has been limited by the absence of appropriate control groups. This study uses linked data from a statewide database in Massachusetts to analyze, for the first time, a large number of ART deliveries and deliveries to patients having the same diagnoses but no ART treatment and to compare deliveries of these diagnosis and treatment groups with deliveries to a fertile population. The data demonstrate that many of the adverse outcomes for ART are also seen in the non-ART deliveries. The data suggest that underlying infertility can result in adverse pregnancy outcomes and that these occur even in the absence of ART treatment.

In a previous study from the MOSART collaborative, we demonstrated that ART births had increased rates of preterm delivery and low birthweight but that deliveries to a defined subfertile population also showed higher risks (6). The subfertile population in that study, identified through a combination of birth certificate information, use of ART for previous deliveries, and hospitalizations that included ICD-9 codes of infertility (9), was not further categorized by specific infertility-related diagnosis. In another study we compared diagnosis categories within the ART population using male factor pregnancies as the reference group and found elevated risks for gestational diabetes and preterm delivery in women with ovulation disorders as well as an increased risk of prenatal hospital admissions for women with endometriosis (5). Diagnoses have also been shown to affect outcome in other studies (12, 13). The current study adds to these prior studies by providing a direct diagnosis-specific comparison between ART and non-ART pregnancies as compared to fertile pregnancies.

All ART and non-ART treated diagnosis categories except those with reproductive inflammation had a higher Cesarean section rate than did deliveries to fertile women. Whether these were the result of more conservative management of “precious pregnancies” (14) or higher rates of complications in high risk pregnancies cannot be determined from these data. Nevertheless, increased rates of Cesarean section have been reported previously for ART pregnancies (4, 15) and it is interesting that the rates were also higher in the comparable non-ART diagnosis groups as well.

Patients with ovulation disorders had a number of adverse outcomes. This is consistent with prior studies (12). Gestational diabetes, hospital admissions, preterm birth and low birthweight were all increased in both the ART treated and non-ART treated groups for this population. A high proportion of this population has the diagnosis of polycystic ovarian syndrome (PCOS) and this disorder, with multiple metabolic abnormalities, is likely a contributor to many of these adverse outcomes. PCOS is associated with hypertensive disorders and diabetes and has been previously shown to increase prematurity (16). These women also frequently produce large numbers of eggs, which has recently been correlated with adverse outcomes of ART pregnancies (17).

Endometriosis also resulted in an increase in adverse outcomes. Endometriosis may cause physical distortion of the reproductive tract, decreased endometrial receptivity and decreased oocyte or embryo quality (18, 19). Although hospital admissions and Cesarean section were more common in both ART and non-ART endometriosis groups, the non-ART group also had increased emergency room visits, observational hospital stays, preterm birth and prematurity. One possible explanation for this difference is that the non-ART pregnancies, diagnosed as they were through hospital admission data, include patients with more severe disease than those identified as endometriosis patients within the SART CORS data.

The diagnosis of male factor was included to test whether ART would result in adverse outcomes when the primary diagnosis for the pregnancies was not a female abnormality. In this regard, the higher rate of Cesarean section was not unexpected if one assumes that this rate may increase in conservatively managed pregnancies compared to those to women of the same age with spontaneous pregnancies, but the increase in preterm delivery and pregnancy induced hypertension were unexpected. While the former may have resulted from the underlying diagnosis that resulted in the male factor infertility (specific diagnoses for which are unavailable in SART CORS) an explanation for the latter is not readily apparent.

ART pregnancies to patients defined as having tubal infertility and non-ART pregnancies to women with reproductive inflammation both showed higher rates of hospital admissions, preterm deliveries and babies with low birthweight as compared to the fertile group. Reproductive inflammation as we have defined it in this study is not a standard infertility diagnosis. Nevertheless, the underlying diagnoses included in this group can all lead to infertility and infecundity and all share a potential for compromised immunity. We included in this group a variety of inflammatory conditions of the uterus, ovaries, and pelvis as well as Fallopian tubes. These conditions can lead to adhesions or scarring of the Fallopian tubes resulting in difficulties getting pregnant but they can also increase rates of infertility and miscarriage without resulting in scarring (20–22). Given the extent of their influence, a more comprehensive analysis of the prevalence of these inflammatory diagnoses in the infertility population and their effect on outcomes may be warranted.

The strength of this study lies in the large numbers of patients included in these analyses and the ability to directly compare ART and non-ART populations. This study also has several limitations. Diagnostic information in the different groups is incomplete. For example, the type of ovulatory disorder and the stage of endometriosis are not delineated in SART CORS or the hospital records of most of the patients. Second, the severity of the diagnoses in the

SART CORS data identified from records at ART clinics may not be as great as in the non-ART groups that were identified from hospital discharges, observational stays, and emergency room visits. This may explain the more extensive adverse outcomes in the non-ART treated groups. In addition, time to pregnancy is not available for any group. We also did not have the ability to study early pregnancy losses given that the linkage we performed was at the level of deliveries. Finally, this study represents results from one location, the state of Massachusetts, and these data may not be representative of the entire U.S. or of other countries.

Conclusion

In conclusion, this study has provided strong evidence for a significant role of underlying infertility-related diagnosis as a major contributing factor to increases in adverse pregnancy and obstetric outcomes of ART deliveries. Continued work is needed to increase our understanding of the causes of these adverse events.

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Table 1

Demographic Profile of Diagnostic Groups With and Without ART Treatment

Factor	Fertile		Male Factor		Endometriosis		P Endo	Ovulation Disorders		P Ov Disord	Tubal	Inflammation	P Tubal/Inf	P All Groups
	No-ART	ART	ART	No-ART	ART	No-ART		ART	No ART					
(N)	297,987	1,901	406	590				676	833		706	2,675		
Mother's Age (mean years, SD)	29.7 (5.8)	34.4 (4.1)	35.2 (3.6)	30.2 (5.7)			<0.0001	33.8 (4.1)	27.2 (5.7)	<0.0001	35.1 (4.0)	25.1 (5.1)	<0.0001	<0.0001
Range	18 – 54	21 – 47	26 – 46	18 – 45				24 – 47	18 – 43		23 – 49	18 – 51		
(%) <35	78.1	49.6	42.4	75.4				59.0	88.0		43.6	93.7		
35–37	13.3	26.2	29.3	13.9			<0.0001	22.9	7.2	<0.0001	27.3	3.6		<0.0001
38–39	4.8	13.7	17.5	6.3				8.1	2.9		14.3	1.3		
40	3.8	10.6	10.8	4.4				9.9	1.9		14.7	1.4		
Father's Age (mean years, SD)	32.6 (6.5)	37.4 (6.0)	36.9 (4.9)	32.9 (6.5)			<0.0001	35.9 (5.0)	30.7 (6.7)	<0.0001	37.0 (5.4)	28.3 (6.9)	<0.0001	<0.0001
Range	18 – 78	22 – 65	25 – 61	18 – 58				25 – 60	18 – 59		24 – 69	18 – 63		
(%) <35	57.8	32.8	31.0	56.1				44.4	61.3		32.9	61.8		
35–37	15.0	23.0	28.1	16.6				23.4	9.7		23.9	4.8		
38–39	6.9	13.7	17.2	5.1			<0.0001	9.2	4.9	<0.0001	14.3	2.9		<0.0001
40	12.3	30.2	22.7	13.7				21.5	9.5		27.6	5.6		
Missing	8.0	0.3	LN	8.5				1.6	14.5		LN	24.8		
Mother's Race/Ethnicity (%)														
White	68.0	86.1	87.2	77.3				87.4	64.8		76.1	48.9		
Asian	7.7	5.9	8.4	5.1			<0.0001	8.3	2.9	<0.0001	6.7	1.6	<0.0001	<0.0001
Other	24.3	8.0	4.4	17.6				4.3	32.3		17.3	49.5		
Father's Race/Ethnicity (%)														
White	63.8	87.7	87.4	70.2				87.4	52.7		76.6	35.1		
Asian	6.7	4.7	7.4	4.6			<0.0001	6.5	2.6	<0.0001	6.2	1.4	<0.0001	<0.0001
Other	22.2	7.4	4.2	18.0				5.0	32.1		15.9	41.2		
Missing	7.3	LN	LN	7.3				LN	12.6		LN	22.4		
Mother's Education (%)														

Factor	Fertile		Male Factor		Endometriosis		P Endo	Ovulation Disorders		P Ov Disord	Tubal	Inflammation	P Tubal/Inf	P All Groups
	No-ART	ART	ART	No-ART	ART	No-ART		ART	No ART					
High School or GED	35.9	9.2	5.7	38.0				8.3	53.4		20.1	72.2		Stern et al. <0.0001
Some College or Associate Degree	22.1	17.7	19.2	28.6			<0.0001	16.9	24.7	<0.0001	24.7	21.0	<0.0001	
Bachelor Degree or Graduate School	42.0	73.2	75.1	33.4				74.9	21.9		55.2	6.8		
Father's Education (%)														
High School or GED	37.7	16.4	17.0	41.5				14.2	49.3		29.5	58.4		<0.0001
Some College or Associate Degree	16.4	15.7	13.6	20.0			<0.0001	15.4	15.5	<0.0001	15.9	12.5	<0.0001	
Bachelor Degree or Graduate School	38.4	67.7	68.5	30.9				69.2	22.2		53.4	6.2		
Missing	7.6	LN	LN	7.6				LN	13.0		LN	22.9		
Pre-existing Maternal Conditions (%)														
Chronic hypertension	1.6	2.2	3.7	2.5			0.30	4.3	4.4	0.89	4.0	1.2	<0.0001	<0.0001
Diabetes mellitus	1.1	1.7	LN	LN			na	4.6	3.4	0.22	2.6	1.8	0.17	<0.0001

LN=Low numbers. Numbers in these cells are suppressed.

na= not calculated due to low numbers.

Table 2

Pregnancy and Delivery Outcomes by Diagnostic Groups With and Without ART Treatment

Factor	Fertile		Male Factor	Endometriosis		P Endo	Ovulation Disorders		P Ov Disord	Tubal	Inflammation	P Tubal/Inflam	P All Groups
	No-ART	ART		ART	No-ART		ART	No ART					
(N)	297,987	1,901	590	406	590		676	833		706	2,675		
Pregnancy Diagnoses (%)													
Pregnancy Hypertension	8.4	15.2	11.0	11.8	11.0	0.69	18.3	11.9	0.0004	13.9	8.2	<0.0001	<0.0001
Gestational Diabetes	5.5	7.5	6.4	6.4	6.4	0.98	14.2	10.8	0.05	10.8	4.8	<0.0001	<0.0001
Bleeding Diagnoses (%)													
Uterine bleeding	0.5	2.6	2.2	5.4	2.2	0.01	3.0	1.9	0.19	3.1	1.4	0.002	<0.0001
Abruptio placenta	0.7	1.7	LN	LN	LN	na	LN	LN	na	LN	0.9	na	<0.0001
Excess bleeding in labor	0.7	1.2	LN	LN	LN	na	2.4	LN	na	LN	0.6	na	0.0004
Placenta previa	0.4	1.6	LN	LN	LN	na	LN	LN	na	1.6	LN	na	<0.0001
Prenatal hospitalization (%)													
Emergency room visits	22.1	13.4	48.0	14.5	48.0	<0.0001	14.8	49.6	<0.0001	18.0	60.5	<0.0001	<0.0001
Observational stays	12.5	14.1	23.6	15.5	23.6	0.002	15.4	24.0	<0.0001	13.9	27.3	<0.0001	<0.0001
Hospital admissions	3.8	6.3	11.9	10.1	11.9	0.38	12.3	11.3	0.55	8.6	11.9	0.02	<0.0001
Labor & Delivery (%)													
Breech/Malpresentation	4.3	13.5	3.7	12.1	3.7	<0.0001	15.5	5.5	<0.0001	13.6	3.2	<0.0001	<0.0001
Cephalopelvic Disproportion	2.6	2.7	3.4	4.2	3.4	0.51	1.8	4.1	0.01	3.1	2.0	0.08	0.07
Mode of Delivery (%)													
Vaginal	65.3	43.1	52.4	40.6	52.4	0.0003	43.5	61.5	<0.0001	41.9	70.2	<0.0001	<0.0001
VBAC	1.3	0.7	LN	LN	LN	na	LN	LN	na	LN	1.0	0.48	0.03
Forceps	0.5	0.6	LN	LN	LN	na	LN	0.0	na	LN	LN	na	0.07
Vacuum	3.6	3.2	2.9	3.5	2.9	0.61	3.4	2.5	0.31	2.8	2.7	0.84	0.08
Primary cesarean	18.7	42.1	29.5	44.6	29.5	<0.0001	41.0	23.3	<0.0001	38.4	16.5	<0.0001	<0.0001
Repeat cesarean	12.8	11.8	15.4	11.8	15.4	0.11	13.3	13.0	0.84	16.7	11.4	<0.0001	0.003
Plurality At Birth (%)													
Singleton	98.6	74.0	LN	72.4	LN	<0.0001	71.0	96.0	<0.0001	75.6	98.9	<0.0001	<0.0001

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Factor	Fertile		Male Factor		Endometriosis		P Endo		Ovulation Disorders		P Ov Disord		Tubal	Inflammation	P Tubal/Inflam	P All Groups
	No-ART	ART	ART	No-ART	ART	No-ART	ART	No ART	ART	No ART	ART	No ART	ART	No ART		
Twins	1.4	26.0	27.6	LN				29.0	4.0				24.4	1.1		
Singleton Pregnancies (N)	293,910	1,406	294	LN				480	800				534	2,646		
Length of gestation (weeks, SD)	39.0 (1.8)	38.8 (1.9)	38.6 (2.1)	38.6 (1.9)			0.97	38.3 (2.4)	38.8 (2.2)		0.0003		38.5 (2.3)	38.6 (2.2)	0.08	<0.0001
Preterm (<37 weeks) (%)	6.2	8.4	8.8	10.3			0.49	13.1	9.1		0.02		11.2	9.9	0.35	<0.0001
Birthweight (grams, SD)	3,369 (548)	3,360 (577)	3,351 (561)	3,331 (599)			0.63	3,238 (634)	3,312 (619)		0.04		3,269 (613)	3,206 (595)	0.03	<0.0001
Low Birthweight (<2,500 g) (%)	5.2	6.6	4.4	7.6			0.08	9.4	7.8		0.31		7.9	9.3	0.29	<0.0001
Birthweight Z-Score (mean, SD)	0.02 (0.97)	0.04 (0.99)	0.08 (0.94)	0.04 (1.01)			0.61	−0.03 (0.96)	−0.00 (1.03)		0.62		0.00 (0.96)	−0.16 (0.99)	0.0005	<0.0001
1.28 (10 th %ile) (%)	8.0	8.0	6.5	8.9			0.21	8.5	9.9		0.43		7.1	11.0	0.01	<0.0001
Twin Pregnancies (N)	4,077	495	112	LN				196	33				172	29		
Length of gestation (weeks, SD)	35.6 (3.1)	35.7 (2.8)	35.8 (2.8)	35.8 (2.5)			0.96	35.2 (3.1)	33.5 (4.9)		0.07		35.7 (2.8)	35.6 (2.8)	0.83	0.05
Preterm (<37 weeks) (%)	52.4	50.9	50.0	50.0			1.00	60.2	69.7		0.30		54.1	55.2	0.91	0.13
Birthweight (grams, SD)	2,402 (613)	2,461 (611)	2,424 (622)	2,452 (531)			0.90	2,376 (617)	2,029 (805)		0.005		2,437 (556)	2,267 (570)	0.13	0.07
0 Low Birthweight (<2,500 g) (%)	37.4	39.6	42.9	37.5			0.29	36.7	LN		0.22		33.7	LN	0.20	0.06
1 Low Birthweight (<2,500 g) (%)	20.6	23.6	17.9	0.0				16.8	LN				25.0	LN		
2 Low Birthweight (<2,500 g) (%)	42.0	36.8	39.9	62.5			0.29 1.00	46.4	57.6		0.22 0.08		41.3	58.6	0.20 0.16	0.06 0.18
Any Low Birthweight (<2,500 g) (%)	62.6	60.4	57.1	62.5				63.3	78.8				66.3	79.3		
Birthweight Z-Score (mean, SD)	−0.62 (0.86)	−0.55 (0.86)	−0.66 (0.97)	−0.49 (0.71)			0.63	−0.51 (0.83)	−0.58 (0.95)		0.69		−0.54 (0.94)	−0.88 (0.86)	0.08	0.10
0 1.28 (10 th %ile) (%)	68.9	71.1	67.9	75.0			0.83	72.5	36.4		0.14		70.9	62.1	0.35	0.68
1 1.28 (10 th %ile) (%)	21.6	21.8	21.4	12.5				21.9	LN				20.4	LN		
2 1.28 (10 th %ile) (%)	9.5	7.1	10.7	12.5			0.83 1.00	5.6	LN		0.14 0.30		8.7	LN	0.35 0.34	0.68 0.78
Any 1.28 (10 th %ile) (%)	31.1	28.9	32.1	25.0				27.6	36.4				29.1	37.9		

LN=Low numbers. Numbers in these cells are suppressed.

na= not calculated due to low numbers.

Table 3

Risk of Adverse Pregnancy and Delivery Outcomes by Diagnosis and Treatment

Outcomes (all pluralities)		Fertile		Male Factor			Endometriosis			Ovulation Disorders			Tubal			Inflammation								
Treatment	No-ART	ART			ART			ART			ART			ART										
	(%)	AOR	(%)	95% CI	(%)	AOR	95% CI	(%)	AOR	95% CI	(%)	AOR	95% CI	(%)	AOR	95% CI	(%)	AOR	95% CI					
MATERNAL OUTCOMES*																								
Pregnancy Hypertension	8.4	1.00	15.2	1.42	1.23, 1.63		11.8	0.90	0.64, 1.26	11.0	1.24	0.94, 1.63	18.3	1.53	1.23, 1.91	11.9	1.09	0.83, 1.42	13.9	1.08	0.84, 1.38	8.2	0.98	0.84, 1.14
Gestational Diabetes	5.5	1.00	7.5	1.15	0.96, 1.38	6.4	0.93	0.62, 1.39	6.4	1.08	0.75, 1.57	14.2	2.17	1.72, 2.73	10.8	1.94	1.52, 2.48	10.8	1.42	1.09, 1.84	4.8	0.88	0.73, 1.06	
Prenatal Hospitalizations																								
Emergency Room Visits	22.1	1.00	13.4	0.89	0.78, 1.03	14.5	1.08	0.80, 1.44	48.0	3.38	2.85, 4.01	14.8	1.01	0.80, 1.26	49.6	2.80	2.42, 3.23	18.0	1.05	0.85, 1.28	60.5	3.42	3.15, 3.71	
Observational Stays	12.5	1.00	14.1	1.12	0.97, 1.28	15.5	1.30	0.99 1.71	23.6	2.02	1.67, 2.46	15.4	1.20	0.96, 1.49	24.0	1.92	1.62, 2.27	13.9	1.07	0.86, 1.34	27.3	2.25	2.06, 2.46	
Hospital Admissions	3.8	1.00	6.3	1.18	0.97, 1.43	10.1	1.97	1.38, 2.80	11.9	3.34	2.59, 4.31	12.3	2.31	1.81, 2.96	11.3	2.56	2.05, 3.21	8.6	1.51	1.14, 2.01	11.9	2.79	2.47, 3.15	
Primary Cesarean Delivery**	21.4	1.00	47.8	1.95	1.75, 2.17	50.6	2.12	1.67, 2.69	34.9	1.93	1.60,2.33	47.3	1.71	1.43, 2.04	26.8	1.27	1.07, 1.51	46.2	1.88	1.57, 2.25	18.7	0.92	0.83, 1.02	
INFANT OUTCOMES*																								
Preterm	6.9	1.00	19.5	1.24	1.07, 1.44	20.2	1.22	0.90, 1.66	10.9	1.66	1.26, 2.18	26.8	1.93	1.55, 2.41	11.5	1.38	1.10, 1.74	21.7	1.47	1.16, 1.85	10.4	1.44	1.27, 1.65	
Low Birthweight	6.0	1.00	20.6	1.27	1.08, 1.48	19.0	0.97	0.70, 1.33	8.3	1.46	1.07, 1.99	25.0	1.60	1.23, 2.06	10.6	1.38	1.09, 1.76	22.1	1.42	1.11, 1.82	10.1	1.54	1.34, 1.76	
Birthweight Zscore 1.28 (SGA)	8.3	1.00	13.5	1.06	0.91, 1.23	13.6	1.05	0.77, 1.43	9.2	1.08	0.81, 1.43	14.1	1.04	0.82, 1.32	10.9	1.16	0.93, 1.46	12.5	0.97	0.77, 1.24	11.3	1.27	1.12, 1.44	

* models adjusted for maternal age, race/ethnicity, education; maternal preexisting medical conditions (chronic hypertension and other diabetes), plurality

** models adjusted for all factors above, as well as breech/malpresentation and cephalopelvic disproportion, and excluding women with prior cesarean delivery