Journal of Assisted Reproduction and Genetics (2018) 35:1585–1593
https://doi.org/10.1007/s10815-018-1238-x

ASSISTED REPRODUCTION TECHNOLOGIES

Birth outcomes of singleton vaginal deliveries to ART-treated, subfertile, and fertile primiparous women

Judy E. Stern[1] · Chia-ling Liu[2] · Howard J. Cabral[3] · Elliott G. Richards[4] · Charles C. Coddington[5] · Sunah Hwang[6] · Dmitry Dukhovny[7] · Hafsatou Diop[2] · Stacey A. Missmer[8,9]

Received: 6 May 2018 / Accepted: 8 June 2018 / Published online: 20 June 2018

Abstract

Purpose To determine whether differences in birth outcomes among assisted reproductive technology (ART)-treated, subfertile, and fertile women exist in primiparous women with, singleton, vaginal deliveries.

Methods Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) data were linked to Massachusetts vital records and hospital discharges for deliveries between July 2004 and December 2010. Primiparous women with in-state vaginal deliveries, adequate prenatal care, and singleton birth at ≥ 20 weeks (n = 117,779) were classified as ART-treated (linked to ART data from SART CORS, n = 3138); subfertile (not ART-treated but with indicators of subfertility, n = 1507); or fertile (neither ART-treated nor subfertile, n = 113,134). Outcomes of prematurity (< 37 weeks), low birthweight (< 2500 g), perinatal death (death at ≥ 20 weeks to ≤ 7 days), and maternal prolonged length of hospital stay (LOS > 3 days) were compared using multivariable logistic regression.

Results Compared to fertile, higher odds were found for prematurity among ART-treated (adjusted odds ratio [AOR] 1.40, 95% confidence interval [CI] 1.25–1.50) and subfertile (AOR 1.25, 95% CI 1.03–1.50) women, low birthweight among ART-treated (AOR 1.41, 95% CI 1.23–1.62) and subfertile (AOR 1.40, 95% CI 1.15–1.71) women, perinatal death among subfertile (AOR 2.64, 95% CI 1.72–4.05), and prolonged LOS among ART-treated (AOR 1.33, 95% CI 1.19–1.48) women. Differences remained despite stratification by young age and absence of pregnancy/delivery complications.

Conclusions Greater odds of prematurity and low birthweight in ART-treated and subfertile, and perinatal death in subfertile deliveries are evident among singleton vaginal deliveries. The data suggest that even low-risk pregnancies to ART-treated and subfertile women be managed for adverse outcomes.

Keywords ART · Subfertile · Outcome · Vaginal delivery · SART CORS

Presented as an abstract at the American Society for Reproductive Medicine Annual Meeting, October 29–November 1, 2017.

✉ Judy E. Stern
judy.e.stern@dartmouth.edu

[1] Department of Obstetrics & Gynecology and Pathology, Dartmouth-Hitchcock, One Medical Center Drive, Lebanon, NH 03756, USA

[2] Mass Department of Public Health, Boston, MA, USA

[3] Department of Biostatistics, Boston University, Boston, MA, USA

[4] Department of Obstetrics and Gynecology, Cleveland Clinic, Cleveland, OH, USA

[5] Department of Obstetrics and Gynecology, Mayo Clinic, Rochester, MN, USA

[6] Section of Neonatology, Department of Pediatrics, University of Colorado School of Medicine, Aurora, USA

[7] Department of Pediatrics, Oregon Health & Science University, Portland, USA

[8] Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA

[9] Department of Obstetrics, Gynecology and Reproductive Biology, Michigan State University, Grand Rapids, MI, USA

Introduction

It is well established that pregnancies utilizing assisted reproductive technology (ART) have a higher prevalence of premature and low birthweight infants, even in singleton deliveries, than pregnancies to women who had no fertility treatment [1–4]. In our prior studies, we have also shown that both ART-treated women and women with indicators of subfertility have more underlying medical pathology that affects pregnancy outcome [5–7].

ART treatment has been shown to be associated with a higher rate of cesarean delivery [8–12]. We have also previously shown higher rates of cesarean delivery among ART-treated (45.7%) and subfertile (43.3%) than fertile (31.3%) women in Massachusetts [13] and have demonstrated that the greater odds of cesarean delivery are largely associated with underlying medical and obstetric factors [6, 11, 13].

Deliveries to ART-treated women have also been reported to have a higher rate of adverse obstetric and perinatal outcomes than deliveries to fertile women who received no fertility treatment, including higher rates of gestational diabetes, pregnancy hypertension, placental abnormalities, and bleeding disorders [10–12, 14–16]. Given that individuals with more underlying pathology are more likely to be delivered by cesarean and that ART-treated and subfertile women also have more pathology than fertile women, it is possible that much of the difference seen overall in ART-treated or subfertile women is found among the cesarean deliveries and that women delivering vaginally, presumably with lower risk of adverse outcomes, do not demonstrate these differences. The goal of this study was to evaluate birth outcomes and maternal hospitalizations in primiparous women with a vaginal, singleton delivery. The secondary goal was to determine whether, within strata of subgroups by maternal age and lack of pregnancy and delivery complications, the differences among fertility groups is eliminated.

Materials and methods

This retrospective cohort study used Massachusetts ART data linked to birth and fetal death records that were further linked to hospital discharges.

Patients The study population included primiparous women in Massachusetts with in-state deliveries occurring between July 1, 2004, and December 31, 2010, that resulted in singleton live birth or fetal death at ≥ 20 weeks who had had a minimum of adequate prenatal care as defined by the Kotelchuck index [17]. We excluded multiparous women and multiple gestation deliveries (312,906 of 486,075 excluded).

Data sources Our data sources and linkages have been described previously [18]. Data were obtained from (1) the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) online database, a national registry containing cycle-based ART data from the majority of US ART clinics and (2) the Massachusetts-based Pregnancy to Early Life Longitudinal (PELL) data system, an ongoing population-based data system that compiles information from birth certificates, fetal death certificates, and hospital utilization data as well as the birth defects registry, cancer registry, and other Massachusetts public programs such as early intervention (EI) and special supplemental nutrition program for women, infant, and child (WIC). The study took place under a memorandum of understanding between SART, the Massachusetts Department of Public Health (MDPH), and the project principal investigators. Institutional review board approval was obtained from MDPH and the Committee for the Protection of Human Subjects at Dartmouth College.

The SART CORS contains comprehensive data from over 90% of all clinics performing ART in the USA; Massachusetts has had between six and eight clinics during the study period, all of which reported data to the SART CORS. Data are collected and verified by SART and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102–493). The database includes information on all forms of ART (those treatments that include manipulation of oocytes and embryos in vitro) regarding demographics, ART diagnoses, ART cycle treatment parameters, and treatment and pregnancy outcomes. Data in the SART CORS are validated annually with some clinics randomly selected for on-site visits during which data reported by the clinic are compared with information recorded in patient charts. In 2013, 35 of a total of 467 clinics were randomly selected for review of 2062 cycles. In these cycles, 10 of 11 fields reviewed had ≤ 3% discrepancy rates for chart information and entries into the database. The 11th field, diagnosis, which was not used in this study, had discrepancy rates of up to 5.5% with underreporting being the most common reason for discrepancy [19].

The PELL data system links information on more than 98% of all births and fetal deaths in Massachusetts to corresponding hospital utilization data (hospital admissions, observational stays, and emergency room visits) for individual women and their children. The MDPH and the Massachusetts Center for Health Information and Analysis are the custodians of the PELL data. PELL is a relational data system composed of individual databases linked together by randomly generated unique IDs for mother and infant. The PELL data system is housed at MDPH.

Linkage of the SART CORS and PELL databases The Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) database was constructed through linkage of the SART CORS and PELL data systems for all Massachusetts resident women delivering in Massachusetts

hospitals between July 1, 2004, and December 31, 2010. We obtained ART cycles for all US women for which there was at least one cycle where the woman had either a Massachusetts residency or ART treatment in the state of Massachusetts. All forms of ART where linked with the exception of gestational carrier cycles. The starting date was chosen based on the availability of SART CORS data (January 1, 2004 cycle starts with first deliveries in July). A deterministic five-phase linkage algorithm methodology was used with matching based on mother's date of birth, her first name and last name, father/partner's last name, baby's date of birth, plurality, and infant gender. Our linkage rate was 89.7% overall and 95.0% for deliveries in which both mother's zip code and clinic were located in Massachusetts [18].

Obstetric and fetal outcomes Outcome measures were prematurity (< 37 weeks gestational age), low birthweight (< 2500 g), small for gestational age (SGA, in live births), perinatal death (fetal death at ≥ 20 weeks plus death of the newborn up to 7 days post-delivery), prolonged maternal length of stay (LOS) following delivery (> 3 days), and maternal hospital readmission (rehospitalizations 0–60 days after delivery plus emergency department [ED] or observational stay [OS] visits 0–7 days after delivery). Gestational age was recorded on the birth and fetal death certificates and was calculated from clinical estimates modified by estimated date of last menstrual period where needed. Birthweight was recorded on the birth certificate and SGA and LGA were calculated from Massachusetts state, sex, and race/ethnicity-specific birthweight means for live births from 1998 to 2010. SGA was defined as *z*-scores for birthweights falling below the 10th percentile for gestation and sex (≤ 1.28 of population-based norms) and LGA was those falling above the 90th percentile (≥ 1.28 of population-based norms) as we have described previously [11]. Perinatal death data were acquired from fetal deaths and linked birth/death certificates. Reasons for perinatal death were abstracted from the diagnosis codes entered for the death and included abnormal tumor markers (R97) or malformations (Q897), extreme immaturity or low birthweight (P072), a variety of delivery complications, and unspecified fetal death (P95). Hospital type among perinatal deaths was determined from discharge records as Level I (basic care), Level II (specialty care), and Level III (subspecialty intensive care). Length of stay for delivery hospitalization and maternal readmission was calculated from PELL hospital admission and discharge dates.

Exposure and stratifying variables Women were classified as ART-treated if the delivery was linked to ART data from the SART CORS online database. They were classified as "subfertile" if they had either a diagnosis of infertility demonstrated by a hospitalization (hospital discharge or observational stay) within 5 years prior to the index delivery that contained an ICD9 code of infertility (628.9 or V23.0) or they had indication on the birth or fetal death certificate of use of non-ART medically assisted reproduction (MAR) [20]. The term subfertility was used rather than infertility or MAR [21] to indicate that this was a combination measure rather than one or the other of these determinations. Women were classified as fertile if they fell into neither the ART-treated nor the subfertile groups. Mode of delivery was determined from the birth certificate. Per inclusion criteria, there were no missing exposure (fertility status) data.

Potential confounding variables Demographic covariates were obtained from the birth/death certificates. Medical history and delivery characteristics were determined from a combination of birth certificates and hospital discharge data. Prior uterine surgery included surgeries prior to calculated conception date with CPT codes of 574.60, 574.61, 578.00, 581.40, 581.45, 585.58, 585.60, 585.61, 591.36, and 591.40, and ICD9 codes of 752.2, 761.4, 68.22, 68.29, and 69.49. Pregnancy and delivery complications identified from checkboxes on the birth certificate and ICD9 codes in hospital discharges included gestational diabetes (ICD9 648.8), pregnancy hypertension (642.3), bleeding (ICD9: 639.1, 640.0, 640.8, 640.9, 641.3, 641.7, 641.8, 641.9), and fetal distress (ICD9: 656.3, 659.7). Placental complications included placental abruption (ICD9: 641.2, 762.1), placenta previa (ICD9: 641.0, 641.1), vasa previa (ICD9: 663.5), and placenta accreta (667.0). Prolonged or dysfunctional labor included ICD9 codes of 661 and 662.0–662.3; breech/malpresentation with ICD9 codes of 652 (excluding 652.1 and 652.5) and 660 (excluding 660.1, 660.6, and 660.7); cord prolapse with ICD9 code of 663.0; premature rupture of membranes (PROM) with ICD9 codes of 761.1 and 658.1–658.3; and cephalopelvic disproportion (CPD) with ICD9 codes of 660.1 and 653.4–653.6.

Statistical analyses Chi-square statistics were used to evaluate the statistical differences in binary outcomes among three fertility groups and ANOVA tests were used to evaluate differences in continuous outcomes. Unconditional logistic regression was applied to quantify crude and adjusted odds ratios (AOR) and 95% confidence intervals (95% CI) for each outcome comparing the ART-treated and subfertile to fertile women or ART-treated to subfertile women. The multivariable models were adjusted for potential confounders including maternal age (≤ 30, 31–34, 35–37, 38–40, > 40), race (Hispanic, non-Hispanic (NH), NH-White, NH-Black, NH-Asian, NH-other race, NH-unknown race), insurance (private, self-pay, public/free), education (≤ high school, some college, ≥ college, unknown education), diabetes (yes, no), chronic hypertension (yes, no), and previous uterine surgery (yes, no), and also potential mediators including gestational diabetes (yes, no in this first pregnancy), pregnancy hypertension

(yes, no in this first pregnancy), pregnancy bleeding (yes, no in this first pregnancy), and placenta complications (any, none in this first pregnancy). The models for placental and bleeding complications, fetal distress, and prolonged/dysfunctional labor adjusted for all of these except the one under study, as well as breech/malpresentation (yes, no), cord prolapse (yes, no), PROM (yes, no), and CPD (yes, no). Women with missing data on maternal age ($n = 1$), marital status ($n = 7$), or insurance ($n = 1$) were excluded from analysis. Heterogeneity by age at delivery and by pregnancy and delivery complications was also evaluated by category-specific stratification as well as formal tests of interaction in our statistical models.

Results

The total population of primiparous, singleton deliveries included 173,169 deliveries of which 117,779 were vaginal and 55,390 cesarean. Of these, the percentage with cesarean deliveries was 45.7% for ART-treated, 43.3% for subfertile, and 31.3% for fertile deliveries. Of premature infants, the percentage with cesarean deliveries was 53.5% for ART-treated, 51.8% for subfertile, and 35.7% for fertile, and of low-birthweight babies, the percentage was 52.2% for ART-treated, 52.7% for subfertile, and 38.0% for fertile deliveries.

The present analysis was restricted to the population with vaginal deliveries which included 117,779 deliveries: 3138 ART-treated, 1507 subfertile, and 113,134 fertile (Table 1). The ART-treated and subfertile women were older, more often White and non-Hispanic, more often college educated, married, and covered by private health insurance than those in the fertile group. ART-treated and subfertile women had more chronic diabetes and hypertension than fertile women as well as a slightly higher proportion with prior uterine surgery.

Prevalence of pregnancy complications differed among the three fertility groups (Table 2). Women with ART-treated and subfertile deliveries had higher prevalence than fertile women of complications, including gestational diabetes, pregnancy hypertension, bleeding problems, and placental complications. There were more premature and low-birthweight deliveries, and more perinatal death in the ART-treated and subfertile groups. Prolonged maternal LOS was higher for ART-treated and subfertile women.

Adjusted odds ratios comparing ART-treated or subfertile women with fertile women are presented in Table 3. There were higher odds of both prematurity and low birthweight among subfertile and ART-treated women. Perinatal death, between 20 weeks and 7 days of birth, was more than two- and a half-fold higher in vaginal births to subfertile women as compared with fertile women but only 28% higher in deliveries to ART-treated women, with the latter being only borderline statistically significant. Maternal prolonged LOS was more common in the ART-treated women while readmission did not differ among groups. There were no significant differences in any outcomes between subfertile and ART-treated women.

Differences in these associations by age at delivery were further explored (Table 4). The percent of deliveries with prematurity increased from 6.8 to 10% between fertile women ≤ 30 and those ≥ 40 years. However, subfertile women had higher odds of prematurity compared to fertile women only among those ≤ 30 years, while ART-treated women had higher odds of prematurity compared to fertile women up to age 34. Low birthweight showed the same pattern, with prevalence increasing with age among the fertile women, but greater odds among subfertile women compared to fertile women only among those ≤ 30 years,

Table 1 Characteristics of primiparous women with singleton, vaginal deliveries: fertile, subfertile, and ART-treated women

	Fertility group		
	Fertile	Subfertile	ART
Number	113,134	1507	3138
Maternal age (years)			
Mean (SD)	27.0 (5.9)	33.4 (4.9)	34.6 (4.5)
Age groups (%)			
≤ 30	70.2	27.9	19.2
31–34	19.7	30.1	31.8
35–37	6.7	21.1	22.9
38–40	2.7	13.7	15.8
> 40	0.8	7.2	10.2
Race/ethnicity (%)			
Hispanic	13.2	4.1	2.9
Non-Hispanic-White	68.5	84.1	85.3
Non-Hispanic-Black	7.4	2.0	2.4
Non-Hispanic-Asian	8.5	8.3	8.3
Non-Hispanic-other	2.3	1.5	1.0
Non-Hispanic-unknown	0.1	0.0	0.1
Education (%)			
≤ High school	35.7	11.0	8.2
Some college	20.2	14.3	13.4
≥ College	44.0	74.6	78.2
Unknown education	0.2	0.1	0.2
Marital status (%)			
Married	60.3	92.8	95.3
Not married	39.7	7.2	4.7
Insurance (%)			
Private	59.8	91.1	95.8
Self-pay	0.9	1.2	1.3
Public/free	39.3	7.6	2.9
Chronic disease (%)			
Diabetes	0.8	1.5	1.7
Hypertension	1.2	1.9	2.3
Uterine surgery prior to conception (%)			
Yes	0.1	0.9	0.5

Table 2 Obstetric and fetal outcomes of primiparous, singleton, vaginal deliveries: fertile, subfertile, and ART-treated women

	Fertility group		
	Fertile	Subfertile	ART
Pregnancy complications			
Gestational diabetes	4.2	7.6	6.8
Pregnancy hypertension	9.4	11.3	11.6
Bleeding problems	2.6	3.6	5.0
Abruptio placenta	0.8	0.9	1.5
Placenta previa	0.2	0.7	0.7
Vasa previa	0.0	0.0	0.0
Placenta accreta	0.6	1.1	1.7
Placental complications (all)	1.6	2.6	3.9
Delivery complication			
Fetal distress	17.8	18.2	19.1
Length of gestation (weeks)			
Mean (SD)	39.0 (2.1)	38.8 (2.6)	38.7 (2.4)
Gestational age (%)			
< 28 weeks	0.6	1.3	1.1
28–33 weeks	1.1	1.6	1.7
34–36 weeks	5.1	5.8	7.3
≥ 37 weeks	93.1	91.3	89.9
Birthweight (g)			
Mean (SD)	3271 (535)	3253 (594)	3229 (579)
Birthweight (%)			
Very low (< 1500 g)	1.0	1.5	1.6
Low (1500–2399 g)	5.1	6.1	6.4
Normal (≥ 2500)	93.9	92.4	92.0
Birthweight *z*-score			
SGA[1]	10.3	9.9	10.2
LGA[2]	5.3	6.6	5.3
Perinatal death			
Fetal + 0–7 days post-delivery	0.7	1.7	0.9
0–7 days post-delivery	0.3	0.7	0.4
Maternal delivery LOS[3]			
Prolonged	9.5	12.9	15.3
Maternal readmission			
Rehospitalization (HD)[4] ≤ 60 days post-delivery discharge	1.4	1.6	1.2
Readmission (ED + OS)[5] ≤ 7 days post-delivery discharge	1.8	1.6	1.3
Combined rehospitalization	3.1	3.2	2.5

Two-sided *p* values quantified by chi-square for binary outcomes and ANOVA for continuous outcomes. All *p* values were < 0.001 except for vasa previa, fetal distress, birthweight *z*-score category, readmission ≤ 7 days post-delivery discharge for which *p* values were > 0.10 (specific results available upon request)

[1] *SGA* small for gestational age at ≤ 1.28 of population-based norms

[2] *LGA* large for gestational age at ≥ 1.28 of population-based norms

[3] *LOS* length of stay; for maternal LOS, standard is discharge within 0–3 days for vaginal deliveries: prolonged is > standard

[4] *HD* hospital discharges

[5] *ED + OS* emergency department and observational stays

while ART-treated women had higher odds of low birthweight compared to fertile women up to age 39. Greater odds of perinatal death were evident for both subfertile and ART-treated compared to fertile women up to 34 years of age. ART-treated deliveries had significantly higher odds of prolonged maternal LOS in all age groups. Both ART-treated and subfertile women had 33% greater odds of prolonged maternal LOS compared to fertile women among those ≤ 30, although for subfertile women, this likelihood was borderline significant.

Differences in these associations according to medical and delivery complications were also quantified (Table 4). Among women with no identified medical, pregnancy, and delivery complications, there continued to be 50% greater odds of prematurity, perinatal death, and prolonged maternal LOS in ART-treated than in fertile women. There were 50% greater odds of low-birthweight babies among subfertile women with no complications, and nearly fourfold greater odds of perinatal death than in fertile women. A three and a half-fold greater odds of perinatal

Table 3 Adjusted odds ratios comparing the obstetric and delivery outcomes of subfertile and ART-treated to fertile women among singleton, vaginal deliveries

	Prematurity (< 37 weeks)		Low birthweight (< 2500 g)		Small for gestational age[2]		Fetal/perinatal death (≥ 20 weeks–7 days)		Perinatal death (0–7 days)		Maternal delivery prolonged LOS		Maternal readmission HD/ED/OS	
	%	AOR (95%CI)[1]	%	AOR (95% CI)[1]	%	AOR (95% CI)[1]	%	AOR (95% CI)	%	AOR (95% CI)[1]	%	AOR (95% CI)[1]	%	AOR (95% CI)[1]
Group														
Fertile	6.9	1.00 (referent)	6.1	1.00 (referent)	10.3	1.00 (referent)	0.7	1.00 (referent)	0.3	1.00 (referent)	9.5	1.00 (referent)	3.1	1.00 (referent)
Subfertile	8.7	1.25 (1.03–1.50)	7.6	1.40 (1.15–1.71)	9.9	0.99 (0.84–1.18)	1.7	2.64 (1.72–4.05)	0.7	3.02 (1.55–5.88)	12.9	1.14 (0.97–1.34)	3.2	1.30 (0.97–1.74)
ART	10.1	1.40 (1.25–1.50)	8.0	1.41 (1.23–1.62)	10.2	1.02 (0.90–1.15)	0.9	1.28 (0.86–1.92)	0.4	1.70 (0.94–3.09)	15.3	1.33 (1.19–1.48)	2.5	1.02 (0.81–1.30)
Subfertile	8.7	1.00 (referent)	7.6	1.00 (referent)	9.9	1.00 (referent)	1.7	1.00 (referent)	0.7	1.00 (referent)	12.9	1.00 (referent)	3.2	1.00 (referent)
ART	10.1	1.22 (0.98–1.52)	8.0	1.07 (0.84–1.35)	10.2	0.99 (0.81–1.22)	0.9	0.61 (0.36–1.05)	0.4	0.68 (0.33–1.41)	15.3	1.17 (0.97–1.41)	2.5	0.79 (0.55–1.15)

LOS length of stay, *HD* hospital discharge, *ED* emergency discharge, *OS* observational stay

[1] *AOR* adjusted odds ratio; multivariable logistic regression adjusted for maternal age, race, insurance, education, marital status, diabetes, chronic hypertension, previous uterine surgery, gestational diabetes, pregnancy hypertension, bleeding, and placental complications

[2] Among live births only

death for subfertile women compared to fertile women was also evident among those with underlying placental complications and bleeding, while within this strata, only ART-treated women had greater odds of prolonged maternal LOS. Among those with fetal distress during labor, subfertility was associated with close to a fivefold greater odds of perinatal death, although the confidence intervals were extremely wide (95% CI 1.07–20.22). Within this complication category, ART-treated women had a significantly greater odds of prematurity and low birthweight compared to fertile women. Among the fetal distress group, neither subfertile nor ART-treated women were associated with maternal prolonged LOS compared to fertile women. No significant associations among the fertility groups were observed with any of the four obstetric or delivery outcomes among women with prolonged or dysfunctional labor.

Heterogeneity and interactions were observed on some outcomes by age at delivery and by pregnancy and delivery complications in stratified analyses (for percentages, see Table 4; statistical testing results available upon request). Specifically, older women in the fertile group were more likely to have preterm or low-birthweight deliveries, whereas the odds reduced in the ART group (although not statistically significant). Similarly, fetal distress was associated with increased odds of having maternal delivery prolonged LOS among the fertile women, but not for the ART women. Moreover, while a prolonged or dysfunctional labor was less likely to occur during a preterm delivery for all the three fertility groups, the odds decreased more significantly among the subfertile group.

Reasons for perinatal death were similar in the different groups; however, the exact numbers in these categories cannot be reported here due to DPH rules on reporting details when the absolute numbers are < 11. Given the very large magnitude of the association between subfertile women and deliveries resulting in perinatal death compared to fertile women, we also reviewed whether the hospital was a low-risk setting or tertiary care facility. In subanalyses, the greater odds of death in the subfertile group did not differ between these two care setting strata (data not shown).

Discussion

Within the population-based cohort of 117,779 singleton vaginal deliveries among primiparous women, we observed that ART-treated and subfertile women had higher odds of prematurity and low birthweight as compared with fertile women. The greater odds among subfertile women was only evident for those < 30, and for ART-treated for those < 34. The greater odds with ART treatment persisted among those with no maternal or placental complications. Perinatal death (≥ 20 weeks gestation to 7 days of life) was most strongly associated with deliveries to subfertile women compared to fertile women, regardless of absence or type of delivery complications.

Table 4 Adjusted odds ratios comparing the obstetric and delivery outcomes of ART-treated and subfertile to fertile women stratified by age of mother and by delivery complications among singleton, vaginal deliveries

	Group	Prematurity (< 37 weeks)		LBW (< 2500 g)		Fetal/perinatal death (≥ 20 weeks–7 days)		Maternal delivery prolonged LOS	
		%	AOR (95% CI)	%	AOR (95% CI)	%	AOR (95% CI)	%	AOR (95% CI)
Age category[1]									
Age ≤ 30	Fertile	6.8	1.00 (referent)	6.2	1.00 (referent)	0.7	1.00 (referent)	8.9	1.00 (referent)
	Subfertile	9.5	1.52 (1.09–2.13)	8.8	1.79 (1.27–2.54)	2.4	5.03 (2.62–9.64)	11.9	1.33 (0.97–1.81)
	ART	12.8	2.11 (1.65–2.71)	9.6	2.02 (1.52–2.67)	1.5	2.80 (1.41–5.58)	11.9	1.33 (1.02–1.72)
Age 31–34	Fertile	6.4	1.00 (referent)	5.4	1.00 (referent)	0.6	1.00 (referent)	9.7	1.00 (referent)
	Subfertile	6.4	0.98 (0.67–1.45)	6.4	1.27 (0.86–1.88)	2.2	3.55 (1.76–7.18)	9.9	1.04 (0.76–1.44)
	ART	9.7	1.53 (1.23–1.91)	7.6	1.49 (1.17–1.91)	1.3	2.03 (1.11–3.72)	11.5	1.23 (1.00–1.51)
Age 35–39	Fertile	7.9	1.00 (referent)	6.7	1.00 (referent)	0.7	1.00 (referent)	12.2	1.00 (referent)
	Subfertile	10.0	1.29 (0.94–1.79)	7.6	1.20 (0.83–1.72)	0.7	1.00 (0.31–3.26)	13.5	1.02 (0.77–1.37)
	ART	9.6	1.24 (0.99–1.55)	8.2	1.29 (1.01–1.63)	0.6	0.89 (0.38–2.09)	16.0	1.33 (1.11–1.59)
Age ≥ 40	Fertile	10.0	1.00 (referent)	8.1	1.00 (referent)	2.0	1.00 (referent)	17.4	1.00 (referent)
	Subfertile	9.2	1.00 (0.58–1.75)	8.1	1.08 (0.59–1.95)	1.2	0.67 (0.15–3.00)	21.4	1.30 (0.86–1.95)
	ART	8.4	0.88 (0.60–1.30)	6.5	0.82 (0.53–1.26)	0.2	0.11 (0.01–0.86)	25.9	1.58 (1.21–2.05)
Pregnancy and delivery complication category									
No complications[2]	Fertile	4.3	1.00 (referent)	4.3	1.00 (referent)	0.6	1.00 (referent)	4.4	1.00 (referent)
	Subfertile	5.3	1.40 (1.00–1.95)	4.9	1.48 (1.05–2.10)	1.8	3.66 (2.04–6.57)	5.6	1.08 (0.78–1.50)
	ART	5.8	1.47 (1.15–1.87)	4.0	1.22 (0.92–1.62)	0.8	1.59 (0.84–2.98)	7.9	1.49 (1.20–1.83)
Placental complications and bleeding[3]	Fertile	17.6	1.00 (referent)	16.0	1.00 (referent)	3.1	1.00 (referent)	16.3	1.00 (referent)
	Subfertile	25.3	1.42 (0.84–2.41)	19.8	1.30 (0.74–2.29)	7.7	3.36 (1.32–8.54)	17.6	0.84 (0.46–1.52)
	ART	19.1	1.08 (0.75–1.55)	16.0	1.11 (0.76–1.62)	1.9	0.63 (0.22–1.83)	26.7	1.55 (1.12–2.14)
Fetal distress[4]	Fertile	5.4	1.00 (referent)	6.0	1.00 (referent)	0.1	1.00 (referent)	12.3	1.00 (referent)
	Subfertile	4.7	0.76 (0.42–1.39)	5.8	1.04 (0.61–1.76)	0.4	4.65 (1.07–20.22)	15.7	1.14 (0.80–1.63)
	ART	9.4	1.62 (1.18–2.22)	9.0	1.55 (1.14–2.11)	0.2	2.14 (0.51–8.88)	15.6	1.08 (0.84–1.39)
Prolonged/dysfunctional labor[5]	Fertile	4.7	1.00 (referent)	4.3	1.00 (referent)	0.3	1.00 (referent)	19.3	1.00 (referent)
	Subfertile	1.6	0.30 (0.07–1.31)	3.2	1.03 (0.36–2.97)	0.0	–	19.8	0.72 (0.43–1.21)
	ART	3.9	1.03 (0.50–2.10)	4.8	1.66 (0.86–3.21)	0.4	3.93 (0.88–17.55)	26.8	1.23 (0.87–1.73)

LBW low birthweight, *LOS* length of stay

[1] Multivariable logistic regression models adjusted for maternal age, race, insurance, education, marital status, diabetes, chronic hypertension, previous uterine surgery, gestational diabetes, pregnancy hypertension, bleeding, and placenta complications

[2] Adjusted for maternal age, race, insurance, education, and marital status

[3.] Adjusted for maternal age, race, insurance, education, marital status, diabetes, chronic hypertension, previous uterine surgery, gestational diabetes, pregnancy hypertension, breech/malpresentation, prolonged labor (> 20 h), dysfunctional labor, fetal distress, cord prolapse, PROM, and cephalopelvic disproportion

[4.] Adjusted for maternal age, race, insurance, education, marital status, diabetes, chronic hypertension, previous uterine surgery, gestational diabetes, pregnancy hypertension, bleeding, placenta complications, breech/malpresentation, prolonged labor (> 20 h), dysfunctional labor, cord prolapse, PROM, and cephalopelvic disproportion

[5.] Adjusted for maternal age, race, insurance, education, marital status, diabetes, chronic hypertension, previous uterine surgery, gestational diabetes, pregnancy hypertension, bleeding, placenta complications, breech/malpresentation, fetal distress, cord prolapse, PROM, and cephalopelvic disproportion

There were greater odds of maternal prolonged LOS in the ART-treated as compared with fertile women; however, maternal readmission did not differ in ART-treated and subfertile women when compared with fertile women.

Previous literature has clearly shown that both prematurity and low birthweight are found more often in ART-treated than in fertile singleton deliveries [1–4]. Our previous studies demonstrated these differences in subfertile deliveries as well [6, 11] and have suggested that underlying infertility also influences these outcomes [5, 7, 11, 22]. In prior studies, we have also sought to understand the extent to which ART treatment versus underlying subfertility conditions are the major drivers of adverse outcomes [22]. To explore this further, the current study evaluated a population of low-risk deliveries. Despite limitation of the study population to these low-risk, singleton, vaginal deliveries of primiparous women, differences in odds of adverse outcomes by fertility groups still persisted.

Previous research has demonstrated that cesarean delivery is more common in ART-treated women than among fertile women [8–12] and our research has also shown this difference to be present in subfertile women [6, 7]. We have further shown that the higher odds of cesarean in ART-treated and subfertile women are largely explained by underlying medical conditions in women who have cesarean deliveries [13]. Data

from this population show that a higher percentage of preterm and low-birthweight babies in the ART-treated and subfertile groups were delivered by cesarean. We expected therefore that the proportion of adverse outcomes among these fertility groups would be lower among these vaginal deliveries. Nevertheless, we still observed greater odds of adverse outcomes when the population was restricted to this presumably low-risk group of singleton, vaginal deliveries. Further, the lowest risk women, those who were younger with no pregnancy and delivery complications, continued to demonstrate these differences in both the ART-treated and subfertile groups. The ART-treated and subfertile women had more chronic diabetes, hypertension, and abnormalities of placentation and bleeding than the fertile women which may contribute to the continued higher odds of prematurity and low birthweight.

A result in this study that was not hypothesized a priori is that the large greater odds of perinatal death in the subfertile but not the ART-treated group, observed by us in previous studies [6, 11], would persist among singleton, vaginal deliveries. Literature on perinatal death after ART has demonstrated mixed results when fertility groups are compared [2, 23]. In the current study, reasons for perinatal death were similar in all the groups and analysis of these reasons did not demonstrate an excess of prematurity in the deaths to the subfertile group as compared with the ART-treated group that would explain this difference. In addition, the greater odds remained pronounced in groups of younger women and women with no underlying medical complications rather than in women > 40 years who might have been expected to have had more complicated deliveries and increased rates of perinatal death in the ART-treated group. Some differences in perinatal death may result from differing definitions in the different studies; however, our results were consistent according to two definitions one that included fetal death and one that did not (Table 3). Prior research has suggested that perinatal death is less common among premature infants with breech presentation delivered by cesarean as compared to vaginal delivery [24], although this result is not supported by all research [25]. It is therefore possible that in these deliveries among presumed high-risk pregnancies, ART-treated women were more quickly considered candidates for cesarean than their subfertile counterparts. Unfortunately, without knowledge of the decision-making that went into the choice of delivery method, we cannot determine this from our data. Also, the extent to which this risk is due to unrecognized placental abnormalities is not known. Subfertile women were no more likely to be delivered in a low-risk setting rather than a tertiary care center but even in the latter setting, they may not have been considered at higher risk as were their ART-treated counterparts.

We previously found differences in severe maternal morbidity between fertility groups [26] but no increase in maternal readmission in ART-treated or subfertile deliveries [27] and no differences in readmission were seen in this study. Even among these vaginal, singleton deliveries, maternal LOS was longer in the ART-treated women compared to fertile women. The greater LOS may again relate to additional unaccounted for maternal complications in these pregnancies. In another study, we also show overall unadjusted child LOS to be higher in ART-treated and subfertile deliveries than in fertile ones (Dukhovny unpublished observations—submitted). It is possible that sicker babies in these groups remain in the hospital longer and their mothers stay with them. However, in another study, we determined that when adjusted for maternal LOS, infant LOS no longer remained significantly different between the groups [28]. Additional studies will be needed to determine which of these factors most contribute to risk.

The strength of this study includes its large sample size comprehensive inclusion of deliveries within the catchment state, and identification of a subfertile population for comparison. Limitations include the use of administrative data that inevitably contain some uncertainty in the coding used to identify underlying medical conditions. We also had no information about details of ICD9 coding for perinatal death nor did we have information on reasons for decisions for maternal hospitalization. We were further limited by lack of information on BMI and on the infertility diagnoses and duration of infertility in the ART-treated and subfertile groups. These unaccounted for factors related to the cause of infertility may define subgroups among the subfertile and ART-treated women that could further differentiate the associations with adverse outcome in these groups. Because the definition of the subfertile group is a conservative one, there may also be subfertile deliveries misclassified into the fertile group; however, our concern was primarily to minimize misclassification in the other direction, inclusion of fertile cases in the much smaller subfertile group. In addition, while internally valid, our data arise from women residing in a single state that has mandated insurance coverage for ART and may not be generalizable to women in every state or country.

In summary, we found that ART treatment and subfertility were associated with higher odds of prematurity and low birthweight even among presumably low-risk singleton vaginal deliveries to primiparous women. The elevated odds of perinatal death in the subfertile group remained higher even when restricted to younger women or those with no placental and delivery complications. Prolonged maternal LOS was greatest in ART-treated women. Our data suggest that deliveries to subfertile women should be considered high risk similar to those of ART-treated women.

Acknowledgments SART wishes to thank all of its members for providing clinical information to the SART CORS database for use by patients and researchers. Without the efforts of our members, this research would not have been possible.

Funding information The work was funded by the National Institute of Child Health and Human Development (RO1HD067270).

Compliance with ethical standards

Institutional review board approval was obtained from MDPH and the Committee for the Protection of Human Subjects at Dartmouth College.

References

1. Schieve LA, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. N Engl J Med. 2002;346:731–7.
2. Helmerhorst FM, Perquin DAM, Donker D, Keirse JNC. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ. 2004;328:261–6.
3. Jackson RA, Gibson KA, Wu YW, Croughan MS. Perinatal outcomes in singletons following in vitro fertilization: a meta-analysis. Obstet Gynecol. 2004;103:551–63.
4. Henningsen AKA, Pinborg A, Lidegaard Ø, Vestergaard C, Forman JL, Andersen AN. Perinatal outcome of singleton siblings born after assisted reproductive technology and spontaneous conception: Danish national sibling-cohort study. Fertil Steril. 2011;95:959–63.
5. Stern JE, Luke B, Tobias M, Gopal D, Hornstein MD, Diop H. Adverse pregnancy and birth outcomes by infertility diagnoses with and without ART treatment. Fertil Steril. 2015;103:1438–45.
6. Declercq E, Luke B, Belanoff C, Cabral H, Diop H, Gopal D, et al. Perinatal outcomes associated with assisted reproductive technology: the Massachusetts Outcomes Study of Assisted Reproductive Technologies (MOSART). Fertil Steril. 2015a;103:888–95.
7. Luke B, Gopal D, Diop H, Stern JE. Perinatal outcomes of singleton siblings: the effects of maternal fertility status and ART treatment. J Assist Reprod Genet. 2016a;33:1203–13.
8. Sullivan EA, Chapman MG, Wang YA, Adamson GD. Population-based study of cesarean section after in vitro fertilization in Australia. Birth. 2010;37:184–91.
9. Romundstad LB, Romundstad PR, Sunde A, von During V, Skjaerven R, Vatten LJ. Assisted fertilization and breech delivery: risks and obstetric management. Hum Reprod. 2009;24:3205–10.
10. Kallen B, Finnstrom, O, Nygren KG, Otterblad Olausson, P, Wennerholm, UB. In vitro fertilisation in Sweden: obstetric characteristics, maternal morbidity and mortality. BJOG 2005; 112: 1529–1535.
11. Luke B, Gopal D, Cabral H, Stern JE, Diop H. Pregnancy, birth, and infant outcomes by maternal fertility status: the Massachusetts Outcomes Study of Assisted Reproductive Technology. Am J Obstet Gynecol. 2017a;217:327.e1–14.
12. Luke B, Gopal D, Cabral H, Stern JE, Diop H. Adverse pregnancy, birth, and infant outcomes in twins: effects of maternal fertility status and infant gender combinations. The Massachusetts Outcomes Study of Assisted Reproductive Technology. Am J Obstet Gynecol. 2017b;217:330.e1–15.
13. Stern, JE, Liu, C, Cabral, H, Richards, EG, Coddington, CC, Missmer, SA Diop, H. Factors associated with the increased risk of cesarean delivery in ART pregnancies. Fertil Steril. 2018 In Press.
14. Hayashi M, Nakai A, Satoh S, Matsuda Y. Adverse obstetric and perinatal outcomes of singleton pregnancies may be related to maternal factors associated with infertility rather than the type of assisted reproductive technology procedure used. Fertil Steril. 2012;98:922–8.
15. Dhalwani, NN, Boulet, SL, Kissin, DM, Zhang, Y, McKane, P, Bailey, MA, Hood, M, Tata, LJ. Assisted reproductive technology and perinatal outcomes: conventional versus discordant-sibling design. 2016; 106: 710–6.
16. Zhu L, Zhang Y, Liu Y, Zhang R, Wu Y, Huang Y, et al. Maternal and live-birth outcome of pregnancies following assisted reproductive technology: a retrospective cohort study. Nature. 2016;6:35141.
17. Kotelchuck M. An evaluation of Kessner adequacy of prenatal care index and a proposed adequacy of prenatal care utilization index. Am J Public Health. 1994;84:1414–20.
18. Kotelchuck M, Hoang L, Stern JE, Diop H, Belanoff C, Declercq ER. The MOSART database: linking the SART CORS clinical database to the population-based Massachusetts PELL reproductive public health data system. Matern Child Health J. 2014;18(9):2167–78.
19. Center for Disease Control and Prevention, American Society for Reproductive Medicine, and Society for Assisted Reproductive Technology. 2013 assisted reproductive technology success rate report: appendix: technical notes Washington, DC: US Dept of Health and Human Services; ftp://ftp.cdc.gov/pub/Publications/art/ART-2013-Clinic-Report-Full.pdf#page=527 (accessed April 28, 2018).
20. Declercq ER, Belanoff C, Diop H, Gopal D, Hornstein MD, Kotelchuck M, et al. Identifying women with indicators of subfertility in a statewide population database: operationalizing the missing link in assisted reproductive technology research. Fertil Steril. 2014;101(2):463–71.
21. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. Fertil Steril. 2017;108:393–406.
22. Luke B, Stern JE, Hornstein MD, Kotelchuck M, Diop H, Cabral H, et al. Is the wrong question being asked in infertility research? J Assist Reprod Genet. 2016b;33:3–8.
23. Ombelet W, Martens G, De Sutter P, Gerris J, Bosmans E, Ruyssinck G, et al. Perinatal outcome of 12 021 singleton and 3108 twin births after non-IVF-assisted reproduction: a cohort study. Human Repro. 2006;21:1025–32.
24. Bergenhenegouwen L, Vlemmix F, Ensing S, Schaaf J, van der Post J, Abu-Hanna A, et al. Preterm breech presentation: a comparison of intended vaginal and intended cesarean delivery. Obstet Gynecol. 2015;126:1223–30.
25. Alfirevic Z, Milan SJ, Livio S. Caesarean section versus vaginal delivery for preterm birth in singletons (review). Cochrane Database Syst Rev. 2013;9
26. Belanoff C, Declercq ER, Diop H, Gopal D, Kotelchuck M, Luke B, et al. Severe maternal morbidity and the use of assisted reproductive technology. Obstet Gynecol. 2016;127:527–34. 26855105
27. Declercq ER, Luke B, Stern JE, Diop H, Gopal D, Cabral H, et al. Maternal postpartum hospitalization following ART births (research letter). Epidemiology. 2015b;26:e64–5.
28. Hwang, SS. Dukhovny, D, Gopal, D, Cabral, H, Missmer, SA, Diop, H, Declercq, E, Stern, JE. Health of infants following ART-treated, subfertile and fertile deliveries in Massachusetts. Pediatrics In press.