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ASSISTED REPRODUCTION TECHNOLOGIES

Perinatal outcomes of singleton siblings: the effects of changing maternal fertility status

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Abstract
Purpose The objective of this study was to evaluate the effect of changing fertility status on perinatal outcomes of singleton siblings, conceived with and without assisted reproductive technology (ART).
Method A longitudinal cohort study of Massachusetts resident women having two consecutive singleton births during 2004–2010 was performed. Women were classified as ART (A), subfertile (S), or fertile (F) and categorized by their fertility status in each birth as A-A, A-S, S-A, S-S, F-A, F-S, and F-F. Within categories, adjusted mean birthweights, gestations, and birthweight *Z* scores were estimated with linear generalized estimating equations. Risks of low birthweight (LBW, <2500 g), preterm birth (PTB, <37 weeks), and placental complications were modeled using logistic regression by fertility status as adjusted odds ratios (AORs) and 95 % confidence intervals (CIs).
Results Birthweights in second pregnancies averaged 74–155 g higher, except for births to F-A women, who averaged −16 g lower. Most women had a reduction in length of gestation in their second pregnancies, with F-A women having the largest decline (−0.5 weeks). In first birth models, the risks for LBW and placental complications were increased for subfertile (AOR 1.39 [1.07–1.81] and 1.97 [1.33–2.93], respectively) and ART women (AOR 1.58 [1.29–1.93] and 3.40 [2.64–4.37], respectively). Second birth models showed increased risks for ART births of LBW (AOR 3.13 [2.19–4.48]) and placental complications (AOR 2.45 [1.56–3.86]) and greater risks of PTB for both ART (AOR 2.37 [1.74–3.23]) and subfertile women (AOR 1.47 [1.02–2.13]).
Conclusions Declining fertility status, with and without assisted reproductive technology treatment, is associated with increasing risks for adverse outcomes, greatest for women whose fertility status declined the most.

Keywords Fertile · Subfertile · Assisted reproductive technology · Infertility · Adverse pregnancy outcomes

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Capsule Declining fertility status, with and without assisted reproductive technology treatment, is associated with increased risk for adverse outcomes.

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Introduction

The outcomes of pregnancies conceived through assisted reproductive technology (ART) have been reported to have lower birthweights and shorter gestations, even when limited to singleton births [1–5].

It is unknown whether these decrements are due to parental characteristics or aspects of the ART treatment: this remains a

primary challenge to infertility research [6–8]. In addition, an acknowledged drawback of prior ART research in the USA has been the self-reported nature of the outcome data, which is typically provided by the patient herself or by her obstetrical provider. Several studies have evaluated pregnancy and birth outcomes in siblings [9–13] but have been limited by either small sample sizes or lack of information on fertility status. This study seeks to overcome these limitations by linking the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System (SART CORS) data to birth certificate and hospital utilization data as well as evaluating repeat pregnancies to the same woman, accounting for fertility status during each pregnancy.

Objective

This analysis is part of a larger population-based study of ART in Massachusetts [14–27]. The objective of this current analysis is to evaluate the effect of maternal fertility status (fertile, subfertile, or ART) on the pregnancy and birth outcomes in consecutive singleton births. The health outcomes of interest include birthweight, birthweight for gestation (*Z* score), small-for-gestation birthweight (*Z* score ≤ -1.28), and low birthweight (<2500 g); length of gestation and preterm birth (<37 weeks); and placental complications (abruptio placenta or placenta previa).

Methods

Study design and setting

This longitudinal cohort study included women whose first two pregnancies resulted in singleton live births of ≥22 weeks of gestation and ≥350 g birthweight in Massachusetts from July 1, 2004, through December 31, 2010. As a project within the Massachusetts Department of Public Health, the Pregnancy to Early Life Longitudinal (PELL) system links records from birth and fetal death certificates, hospital discharges, and program data from child health and development programs.

Data sources

The PELL data system

The PELL system has linked information on more than 99 % of all births and fetal deaths in Massachusetts from 1998 to 2010 to corresponding hospital utilization data (hospital admissions, observational stays, and emergency room visits) for individual women and their children, including 1,004,320 deliveries. The Massachusetts Department of Public Health (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 SART CORS

The data source for ART data for this study was the SART CORS, which contains comprehensive data from more than 85 % of all clinics performing ART and more than 95 % of all ART cycles in the USA. 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). SART maintains HIPAA-compliant business associate agreements with reporting clinics. In 2004, following a contract change with CDC, SART gained access to the SART CORS data system for the purposes of conducting research. The national SART CORS database for 2004–2010 contains 930,957 ART treatment cycles. The database includes information on demographic factors (age, race/ethnicity), ART factors (infertility diagnoses, oocyte source and state, use of micromanipulation, number of embryos transferred), treatment outcomes (number of fetal heart beats on early ultrasound, early pregnancy loss), and pregnancy outcomes (live born, stillborn, length of gestation, plurality, genders). The data in the SART CORS are validated annually [28] with some clinics having on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. In 2012, records for 2045 cycles at 35 clinics were randomly selected for full validation, along with 238 egg/embryo banking cycles [28]. The full validation included a review of 1318 cycles for which a pregnancy was reported. Among the non-donor cycles, 331 were multiple-fetus pregnancies. Ten out of 11 data fields selected for validation were found to have discrepancy rates of ≤5 %. The exception was the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.1 and 9.2 %.

Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART)

The MOSART project links data from the SART CORS with the PELL data system to evaluate pregnancy and child health outcomes on a population basis. A memorandum of understanding was executed between SART and the three entities that participated in the PELL project: Boston University, the Massachusetts Department of Public Health, and the Centers for Disease Control and Prevention. Human subjects approval was obtained from all entities and participating universities. The study also had the approval of the SART Research Committee.

We constructed the MOSART database by linking the SART CORS and PELL data systems for all Massachusetts births to Massachusetts resident women between July 1, 2004, and December 31, 2010. The starting date was chosen based on the availability of SART CORS data (January 1, 2004) to allow us to capture any births associated with ART and the end date reflected the latest available linked data of the SART CORS to PELL. A deterministic five-phase linkage algorithm methodology was implemented [14] using mother's first and last names, mother's date of birth, father's name, race of both parents, date of delivery, and number of babies born per delivery. Linked files were later identified by the use of a linkage ID from which identifiers were removed. The linkage rate was 95.0 % for deliveries in which both zip code and clinic were located in MA. The linkage yielded deliveries identified for this study as *ART deliveries*.

We identified a subfertile group as previously described [15]. Briefly, all Massachusetts deliveries were reviewed for the answer to two questions on the Massachusetts birth certificate about the use of fertility drugs and assisted reproduction. Those who answered "yes" to either or both of these questions and had not been identified in the SART CORS linkage were included as *subfertile*. In addition, any woman who at delivery, or in the 5 years previous to delivery, had been hospitalized with a discharge code of female infertility (International Classification of Diseases (ICD) diagnosis code 628.0, Infertility-Anovulation; 628.2, Infertility-Tubal Origin; 628.3, Infertility-Uterine Origin; 628.8, Female Infertility of other specified origins; 628.9, Female Infertility of unspecified origin or CPT procedural code V230, Pregnancy With Diagnosis of Infertility) was also included as part of the *subfertile group* if they were not in the SART CORS linkage. Deliveries not in either the subfertile or ART groups were listed as *fertile*.

We limited the study population to women whose first two consecutive live births were singletons with gestations ≥22 weeks and birthweights ≥350 g, and grouped them by their fertility status in each of the two pregnancies as fertile-fertile (F-F), fertile-subfertile (F-S), and fertile-ART (F-A); subfertile-subfertile (S-S) and subfertile-ART (S-A); and ART-subfertile (A-S) and ART-ART (A-A). The pairs of pregnancies were then grouped by fertility status at the first pregnancy (fertile, subfertile, and ART).

Variables

Independent variables included parental ages, race and ethnicity, and education; maternal pre-pregnancy medical conditions (chronic hypertension and diabetes mellitus); preeclampsia; gestational diabetes; primary and repeat cesarean birth; and infant gender. Dependent variables included birthweight, birthweight-for-gestation *Z* score, small-for-gestation birthweight (i.e., *Z* score ≤−1.28), and low birthweight (<2500 g); length of gestation and preterm birth (<37 weeks); and placental complications (abruptio placenta or placenta previa).

We created composite variables each for gestational diabetes, diabetes mellitus, chronic and pregnancy-related hypertension, and placenta previa and abruptio placenta using data from the birth certificate and hospital discharge delivery records: ICD-9 648.8 for gestational diabetes; ICD-9 648.0 or 250 for diabetes mellitus; ICD-9 401, 402, 403, 404, or 405 for chronic hypertension; ICD-9 642 for pregnancy-related hypertension; ICD-9 641.0 or 641.1 for placenta previa; ICD-9 641.2 for abruptio placenta.

Parental factors

Factors obtained from the birth certificate included parental ages at delivery, race/ethnicity, and education. Parental age was evaluated as a continuous variable. Parental race/ethnicity was categorized as white, black, Asian, Hispanic, and other. Parental education was categorized as ≤high school or General Educational Development (GED) diploma, some college or associate degree, or bachelor's degree or graduate school.

Length of gestation and prematurity

Length of gestation was calculated by using the birth certificate delivery date minus the date of last menstrual period (LMP) corrected for clinical estimate at early ultrasound. For ART pregnancies, the calculated LMP entered on the birth certificate has been determined by the clinical staff from the date of transfer. Clinical estimate is used to adjudicate any discrepancies. Deliveries prior to 37 completed weeks of gestation were classified as premature and those which were 37 weeks or greater were classified as term.

Low birthweight and small-for-gestational age birthweight

Birthweight was obtained from the birth certificate. Birthweights at each gestational age are normally distributed, and a *Z* score (or standard deviation score) is the deviation of the value for an individual from the mean value of the reference population divided by the standard deviation for the reference population [29]. Birthweight *Z* scores were calculated to evaluate the adequacy of weight for age using population-based standards, as recommended by Land [30] and modeled as continuous and categorical variables. We generated gender-, race/ethnicity-, and gestation-specific birthweight means and standard deviations using the Massachusetts data for all live births from 1998 to 2010. Infants with *Z* scores ≤−1.28 (below the

10th percentile for gestation) were classified as small for gestational age (SGA). Birthweights which were less than 2500 g were classified as low birthweight (LBW).

Statistical methods

Within each fertility status group at the first pregnancy (fertile, subfertile, and ART), we compared maternal and paternal demographic characteristics, pre-pregnancy diagnoses, and perinatal outcomes using Student's *t* test for continuous variables and chi-square test for categorical variables (Tables 1 and 2). Mean birthweight, length of gestation, and birthweight *Z* score were calculated at the first and second births for each fertility status combination, as unadjusted and adjusted in the first birth for maternal age and infant gender and in the second birth for maternal age in the second birth and infant gender, and presented as least square means and standard errors (Table 3). Differences were compared across (F-F), (F-S), and (F-A) groups; between (S-S) and (S-A) groups; and between (A-S) and (A-A) groups. Mean birthweight, gestation, and birthweight *Z* scores were estimated with linear generalized estimating equations, adjusted for maternal age, birth order, and infant gender. Means and standard deviations are reported. For adjusted models, least square means and standard errors are reported. An interaction term between birth order and fertility group were used to estimate differences.

The association between fertility status in the first pregnancy and the risks of low birthweight, preterm birth, small-for-gestation birthweight, and abruptio placenta or placenta previa was computed as odds ratios and 95 % confidence intervals from multivariate logistic regression models as (1) unadjusted and (2) adjusted for maternal age, race and ethnicity, education, and infant gender at the first birth. The association between fertility status in the second pregnancy and the risks of low birthweight, preterm birth, small-for-gestation birthweight, and abruptio placenta or placenta previa was computed as odds ratios and 95 % confidence intervals from multivariate logistic regression models as (1) unadjusted; (2) adjusted for maternal age, race and ethnicity, education, and infant gender at the second birth; and (3) adjusted for maternal age, race and ethnicity, education, infant gender at the second birth, and fertility status at the first birth (fertile, subfertile, or ART) (Table 4). Results were considered significant with p values <0.05 for univariate analyses and when the 95 % confidence intervals did not include 1. All analyses were performed using the SAS software, version 9.2 (SAS Institute).

Results

Descriptive and outcome data

The descriptive statistics of the 59,764 study women by the fertility status group are shown in Table 1. There were 57,384 women whose first pregnancy was classified as fertile, 892 as subfertile, and 1488 as ART. Among women who were classified as fertile in their first pregnancy, those who were also fertile in their second pregnancy (F-F) were the most racially and ethnically diverse, with a lower percent of women who were white and a higher percent who were Hispanic, black, or Asian compared to women whose second pregnancy was classified as subfertile (F-S) or ART (F-A). The racial and ethnic distribution of women whose first pregnancy was classified as subfertile [(S-S) and (S-A)] or ART [(A-S) or (A-A)] did not differ statistically. Maternal education differed significantly within each of the three fertility status groups, with F-F women least likely to have completed college and F-A, S-A, and A-A women most likely to have completed college. Compared to women whose second pregnancy was either fertile or subfertile, women whose second pregnancy was ART were significantly older and had a longer time span between pregnancies; maternal age was controlled for in the multivariate models. Women with both pregnancies classified as ART (A-A) had evidence of a declining clinical situation, with a significantly greater use of donor oocytes, thawed embryos, more than one embryo transferred, and a higher prevalence of diagnoses (particularly diminished ovarian reserve, increasing from 7.9 to 13.6 %). Comparing second births classified as ART, women with A-A compared to women with F-A and S-A, were more likely to use donor oocytes (10.8 % compared to 4.7 % and 8.6 %, respectively) and thawed embryos (32.0 % compared to 7.1 % and 16.2 %, respectively) as well as to have the highest prevalence of the diagnoses of male factor, endometriosis, diminished ovarian reserve, and tubal factors.

The perinatal outcomes by the fertility status groups are shown in Table 2. Among women whose first birth was classified as fertile, those whose fertility status declined with their second birth (F-S and F-A) had twice the rate of gestational diabetes in their second pregnancy, a pattern not evident in any other group. Women whose second birth was classified as ART had the highest prevalence of abruptio placenta or placenta previa, rates that doubled among women whose fertility status had declined in their second pregnancy (F-A and S-A). The highest rates of small-for-gestation birthweight were among women whose fertility status would decline in their second pregnancy (F-A, S-A) as well as in the first pregnancy of women with both pregnancies classified as ART.

Table 1 Description of the study groups

Categories	Fertility status at first birth							*p* value			
	Fertile			Subfertile		ART		Within groups			Across groups
	F-F	F-S	F-A	S-S	S-A	A-S	A-A	Fertile	Subfertile	ART	F-A vs S-A vs A-A
N (pairs)	56,755	249	380	787	105	635	853				
Maternal											
Race/ethnicity (%)											
White	74.0	86.8	91.3	85.5	91.4	88.0	88.5	<0.0001	0.20	0.17	
Hispanic	10.7	2.0	1.8	3.7	1.0	2.4	2.4				
Black	5.9	1.2	1.6	2.1	0.0	1.4	2.9				
Asian	7.4	8.0	5.0	7.4	7.6	7.4	5.3				
Other	2.0	2.0	0.3	1.3	0.0	0.8	0.9				
Education (%)											
High school/GED	29.9	8.0	5.2	9.7	1.9	7.2	4.2	<0.0001	0.002	0.02	
Some college/AA	18.4	12.9	11.6	14.6	7.6	15.1	13.6				
BA/BS/grad school	51.7	79.1	83.2	75.7	90.5	77.7	82.2				
Age at delivery (mean years (SD))											
First birth	27.6 (5.6)	32.0 (4.6)	33.0 (4.2)	32.4 (4.3)	34.2 (4.0)	33.4 (3.8)	34.3 (4.2)	<0.0001	<0.0001	<0.0001	
Second birth	30.1 (5.6)	34.9 (4.6)	36.4 (4.0)	34.6 (4.4)	37.1 (3.9)	35.3 (3.8)	36.7 (4.2)	<0.0001	<0.0001	<0.0001	
Difference	2.4	2.9	3.4	2.2	2.9	1.9	2.4				
Pre-pregnancy diagnoses (%)											
Chronic hypertension											
First birth	1.3	1.2	3.4	1.8	2.9	1.4	2.3	0.0008	0.45	0.20	
Second birth	1.3	1.6	2.9	2.3	3.8	1.4	1.3	0.02	0.34	0.83	
Diabetes mellitus											
First birth	0.8	0.8	0.3	1.5	3.8	1.1	1.8	0.51	0.10	0.30	
Second birth	1.1	1.6	1.1	1.7	1.9	1.4	1.8	0.70	0.85	0.61	
ART factors (%)											
Oocyte source donor											
First birth	–	–	–	–	–	3.0	9.0	–	–	–	
Second birth	–	–	4.7	–	8.6	–	10.8	–	–	–	0.003
State-frozen embryo											
First birth	–	–	–	–	–	8.7	10.2	–	–	–	
Second birth	–	–	7.1	–	16.2	–	32.0	–	–	–	<0.0001
Embryos transferred >1											
First birth	–	–	–	–	–	8.7	10.2	–	–	–	
Second birth	–	–	7.1	–	16.2	–	32.0	–	–	–	<0.0001
Number of fetal heartbeats >1											
First birth	–	–	–	–	–	6.0	7.1	–	–	–	
Second birth	–	–	12.4	–	3.0	–	6.7	–	–	–	0.0004
Infertility diagnosis (%)											
Male factor	–	–	26.6		28.6	30.4	39.8	42.7			<0.0001
Endometriosis	–	–	4.7		3.8	9.1	8.4	8.6			0.02
Ovulation disorders	–	–	14.0		22.9	15.0	14.7	15.1			0.08
Diminished ovarian reserve	–	–	12.6		9.5	5.7	7.9	13.6			0.49
Tubal factors	–	–	10.0		5.7	8.8	10.9	10.9			0.25
Uterine factors	–	–	1.6		4.8	2.1	2.6	2.7			0.17
Other factors	–	–	15.5		14.3	14.2	14.2	11.4			0.12
Unexplained	–	–	30.3		28.6	30.1	21.7	19.7			0.0001

Table 2 Description of perinatal outcomes by fertility status groups

Perinatal outcomes	Birth order	Fertility status at first birth							*p* value		
		Fertile			Subfertile		ART		Within groups		
		F-F	F-S	F-A	S-S	S-A	A-S	A-A	Fertile	Subfertile	ART
N (pairs)		56,755	249	380	787	105	635	853			
Preeclampsia (%)	First birth	1.2	0.8	0.5	1.5	4.8	1.4	1.6	0.44	0.02	0.73
	Second birth	0.7	0.8	1.1	1.9	1.0	0.5	1.3	0.64	0.49	0.11
Gestational diabetes (%)	First birth	4.1	2.8	3.7	8.1	3.8	6.5	6.5	0.53	0.12	0.99
	Second birth	5.2	6.8	7.4	7.1	3.8	6.0	7.2	0.08	0.20	0.37
Abruptio placenta or placenta previa (%)	First birth	1.4	1.6	1.8	3.2	1.9	6.6	4.3	0.70	0.47	0.05
	Second birth	1.6	1.6	4.7	1.7	4.8	2.4	5.0	<0.0001	0.03	0.008
Primary cesarean birth (%)	First birth	30.2	37.8	42.9	39.4	45.7	44.3	39.9	<0.0001	0.21	0.09
	Second birth[a]	8.1	10.3	15.3	10.7	14.0	9.6	14.4	0.0003	0.45	0.03
Repeat cesarean birth (%)	Second birth[b]	79.4	87.2	82.8	82.6	83.3	79.0	85.3	0.10	0.90	0.04
Infant gender (% male)	First birth	51.5	46.2	53.4	50.8	49.5	55.1	51.9	0.19	0.80	0.22
	Second birth	51.3	45.4	49.2	51.2	49.5	52.3	51.6	0.13	0.75	0.79
Preterm birth (%)	First birth	6.4	10.0	6.3	7.5	8.6	9.8	10.0	0.07	0.70	0.90
	Second birth	4.6	8.0	8.2	4.7	6.7	4.7	9.3	0.0002	0.38	0.0009
Low birthweight (%)	First birth	5.6	6.8	6.1	6.4	10.5	7.2	7.9	0.62	0.12	0.66
	Second birth	3.3	5.6	6.1	3.1	7.6	1.4	6.7	0.002	0.02	<0.0001
Small-for-gestation (%) birthweight *Z* score ≤−1.28	First birth	9.7	9.6	11.8	9.4	10.5	8.2	9.7	0.38	0.72	0.30
	Second birth	5.4	4.4	6.3	4.7	3.8	3.6	5.3	0.58	0.68	0.13

[a] The denominator is all vaginal births in first births

[b] The denominator is all births delivered by cesarean in the first birth

Table 3 Models of perinatal outcomes by fertility status within families

Factors	Categories	Fertility status at first birth							*p* value		
		Fertile			Subfertile		ART		Within groups		
		F-F	F-S	F-A	S-S	S-A	A-S	A-A	Fertile	Subfertile	ART
N (pairs)		56,755	249	380	787	105	635	853			
Birthweight (mean g (SD))	First birth	3336 (539)	3311 (544)	3368 (593)	3340 (518)	3270 (610)	3299 (590)	3283 (567)	0.45	0.26	0.59
	Second birth	3435 (512)	3420 (555)	3380 (578)	3465 (506)	3408 (563)	3462 (457)	3378 (572)	0.18	0.33	0.002
Birthweight (mean g (SE))	Difference, unadjusted	98 (2)	108 (37)	12 (32)	124 (19)	138 (60)	162 (23)	95 (21)			
Least-squares means (SE)	Adjusted first birth	3347 (2)	3285 (34)	3323 (30)	3344 (19)	3269 (57)	3301 (24)	3284 (19)	0.17	0.24	0.52
	Adjusted second birth	3421 (2)	3366 (35)	3307 (30)	3460 (19)	3397 (54)	3456 (18)	3365 (20)	<.0001	0.25	0.001
	Difference	74 (2)	81 (36)	−16 (32)	116 (20)	128 (57)	155 (24)	81 (22)			
Length of gestation (mean weeks (SD))	First birth	39.13 (1.81)	38.95 (1.78)	39.10 (1.93)	38.98 (1.71)	38.79 (2.10)	38.75 (2.15)	38.77 (2.04)	0.27	0.37	0.85
	Second birth	39.00 (1.50)	38.70 (1.60)	38.59 (1.80)	38.89 (1.38)	38.58 (1.80)	38.83 (1.30)	38.53 (2.01)	<.0001	0.09	0.0004
Length of gestation (mean weeks (SE))	Difference, unadjusted	−0.17 (0.01)	−0.29 (0.12)	−0.52 (0.11)	−0.10 (0.06)	−0.21 (0.21)	0.08 (0.08)	−0.24 (0.08)			
Least-squares means (SE)	Adjusted first birth	39.10 (0.01)	38.90 (0.11)	39.07 (0.10)	38.99 (0.06)	38.79 (0.20)	38.78 (0.09)	38.79 (0.07)	0.09	0.32	0.96
	Adjusted second birth	38.90 (0.01)	38.60 (0.10)	38.53 (0.09)	38.88 (0.05)	38.55 (0.17)	38.83 (0.05)	38.50 (0.07)	<.0001	0.08	0.0006
	Difference	−0.19 (0.01)	−0.31 (0.12)	−0.55 (0.11)	−0.11 (0.07)	−0.23 (0.21)	0.05 (0.09)	−0.28 (0.09)			
Birthweight *Z* score (mean (SD))	First birth	−0.11 (0.95)	−0.10 (0.94)	−0.08 (1.03)	−0.07 (0.92)	−0.15 (0.96)	−0.08 (0.91)	−0.12 (0.91)	0.88	0.4	0.46
	Second birth	0.13 (0.95)	0.20 (0.99)	0.12 (0.97)	0.19 (0.96)	0.20 (0.90)	0.19 (0.87)	0.15 (0.93)	0.55	0.94	0.41
Birthweight *Z* score (mean (SE))	Difference, unadjusted	0.24 (0.00)	0.31 (0.06)	0.20 (0.05)	0.26 (0.03)	0.35 (0.09)	0.27 (0.04)	0.27 (0.03)			
Least-squares means (SE)	Adjusted first birth	−0.09 (0.00)	−0.14 (0.06)	−0.14 (0.05)	−0.07 (0.03)	−0.16 (0.09)	−0.08 (0.04)	−0.12 (0.03)	0.58	0.43	0.41
	Adjusted second birth	0.12 (0.00)	0.12 (0.06)	0.02 (0.05)	0.19 (0.03)	0.19 (0.09)	0.19 (0.03)	0.14 (0.03)	0.07	0.95	0.37
	Difference	0.21 (0.00)	0.26 (0.06)	0.16 (0.05)	0.26 (0.04)	0.34 (0.09)	0.27 (0.04)	0.26 (0.03)			

Adjusted first birth = maternal age in first birth and infant gender; adjusted second birth = maternal age in second birth and infant gender

Table 4 Models of perinatal outcomes by fertility status and birth order

Models	Group	Number	Low birthweight		Preterm birth		Small-for-gestation birthweight		Abruptio placenta or placenta previa	
			OR/AOR	95 % CI	OR/AOR	95 % CI	OR/AOR	95 % CI	OR/AOR	95 % CI
First birth group status										
Unadjusted	Fertile	57,384	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Subfertile	892	1.25	0.96, 1.62	1.20	0.94, 1.54	0.98	0.78, 1.22	2.24	1.52, 3.30
	ART	1488	1.40	1.15, 1.70	1.60	1.34, 1.90	0.93	0.77, 1.11	4.02	3.17, 5.10
Adjusted 1A	Fertile	57,384	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Subfertile	892	1.39	1.07, 1.81	1.23	0.96, 1.58	1.02	0.82, 1.29	1.97	1.33, 2.93
	ART	1488	1.58	1.29, 1.93	1.63	1.36, 1.95	0.97	0.81, 1.17	3.40	2.64, 4.37
Second birth group status										
Unadjusted	Fertile	56,755	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Subfertile	1671	0.84	0.63, 1.13	1.14	0.91, 1.42	0.77	0.61, 0.98	1.20	0.84, 1.71
	ART	1338	2.04	1.64, 2.55	1.99	1.64, 2.41	1.01	0.79, 1.28	3.19	2.47, 4.11
Adjusted 1A	Fertile	56,755	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Subfertile	1671	1.02	0.76, 1.38	1.22	0.98, 1.53	0.86	0.68, 1.10	1.05	0.73, 1.51
	ART	1338	2.63	2.08, 3.32	2.16	1.76, 2.64	1.18	0.92, 1.51	2.67	2.03, 3.50
Adjusted 2A	Fertile	56,755	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Subfertile	1671	1.15	0.72, 1.84	1.47	1.02, 2.13	0.95	0.62, 1.45	1.04	0.59, 1.84
	ART	1338	3.13	2.19, 4.48	2.37	1.74, 3.23	1.33	0.92, 1.93	2.45	1.56, 3.86

Adjusted 1A = maternal age in current birth, race/ethnicity, education, and infant gender in current birth; adjusted 2A = maternal age in second birth, race/ethnicity, education, infant gender in second birth, and fertility status group for first birth

Table 3 shows the unadjusted and adjusted means and differences in means in birthweight, length of gestation, and birthweight *Z* scores by the seven fertility status combinations. Mean first pregnancy birthweights differed by only about 100 g (from 3270 to 3368 g) and second pregnancy birthweights by about 87 g (from 3378 to 3465 g). Within groups, the difference in birthweights between first and second pregnancies ranged from 95 to 162 g unadjusted and 74 to 155 g adjusted, except for the births to F-A women, who averaged 12 g unadjusted and −16 g adjusted. Most groups had a reduction in length of gestation from the first to second pregnancies, with the F-A group having the largest decline (−0.5 weeks, unadjusted and adjusted).

The risks for adverse outcomes by fertility status and birth order are shown in Table 4. In the first birth-adjusted models, the risks for low birthweight were increased for subfertile and ART women, significantly so for both groups in the adjusted models; the risks for abruptio placenta or placenta previa were also significantly greater for subfertile and ART women, with higher risks in the latter group. The second birth-unadjusted and birth-adjusted models showed significantly greater risks for low birthweight, preterm birth, and abruptio placenta or placenta previa for ART births; the adjusted model also showed a greater risk of preterm birth for subfertile women. The risks were consistently greater for ART versus subfertile births.

Discussion

These findings indicate that subfertile women, with and without ART, are at greater risk for adverse pregnancy outcomes compared to the pregnancy outcomes of fertile women. This analysis also showed that women whose fertility status declined from their first to second (singleton) pregnancy had increased risks for adverse outcomes, greatest for women whose fertility status declined the most (F-A women).

Our findings of an increased risk for placenta previa or abruptio placenta with ART (AOR 3.40, 95 % CI [2.64–4.37] in first births and 2.45 [1.56–3.86] to 2.67 [2.03–3.50] in second births) are in accordance with previous studies [10, 31–33], suggesting that this complication may be related to the technique of embryo transfer, with implantation occurring lower in the uterus with IVF. This may not completely explain the etiology of placental complications, as we found a twofold increased risk in first births among subfertile women (AOR 1.97, 95 % CI 1.33–2.93), who conceived without ART.

Donor oocytes, which could only be utilized in the ART group, help to overcome the issues of older maternal age [34] and maternal obesity [35] but have been associated with greater risks for gestational hypertension and preeclampsia [36–38]. These hypertensive disorders, in turn, are associated with greater risks for placental abruption as well as disseminated intravascular coagulation, cerebral hemorrhage, and

hepatic and renal failures [39]. The risk of hypertensive disorders is also increased with the use of frozen embryos (also only possible in the ART group), even within the same mother [40]. Frozen embryos were used in the second births in this study population in 7.1 % of F-A, 16.2 % of S-A, and 32.0 % of A-A; preeclampsia occurred in 1.1 %, 1.0 %, and 1.3 % of these women, respectively.

Our findings of small differences between sibling birthweights are also in line with prior reports [11]. We were able to refine these differences further, with stratification by changes in fertility status between first and second pregnancies. Among women whose fertility status remained the same in both pregnancies (F-F, S-S, A-A), the difference in first and second birthweights ranged from 74 to 116 g (adjusted). Among women whose fertility status declined (F-S, S-A), the difference in first and second birthweights ranged from 81 to 128 g (adjusted). Women whose fertility status declined the most (F-A) had the most pronounced change in birthweight, with an average reduction of −16 g, as well as the largest reduction in mean length of gestation (−0.55 weeks) and the smallest difference in birthweight *Z* score (0.16) of all fertility groups. Conversely, the only group to show an improvement in fertility status from first to second pregnancy (A-S) had the largest increase in birthweight (155 g) and birthweight *Z* score (0.27). It is important to consider in evaluating these results that transfer of more than one embryo and the use of donor oocytes and thawed embryos (see Table 1) may also have affected the results in the ART-treated pregnancies.

Age is the single most important factor affecting a woman's chance of a live birth. Fecundity declines gradually but significantly beginning at about age 32 and more rapidly after age 37 [41]. This decline reflects both a decrease in egg quality and circulating anti-Müllerian hormone and inhibin B concentrations and a gradual increase in the circulating level of follicle-stimulating hormone. According to data from the 2013 Assisted Reproductive Technology National Summary Report [42], among women using fresh autologous oocytes, the percent of cycles resulting in pregnancy declined from 46 % for women younger than 35 years, to 29 % for women of ages 38–40 years, to 4 % for women older than the age of 44 years. The chances of a live birth fell in a similar pattern: 40 % for women younger than 35 years, to 21 % for women of ages 38–40 years, to 2 % for women older than the age of 44 years. Likewise, miscarriage rates rise with advancing age, from 15 % for women aged 36 years and younger to 29 % at the age of 40 years, to 50 % at the age of 44 years and older [42]. It is estimated that ART compensates for only half of the births lost by postponing a first attempt of pregnancy from 30 to 35 years of age and less than 30 % after postponing from 35 to 40 years of age [43].

The presence of chronic disease prior to pregnancy has been associated with an increased risk for hemorrhage in twin gestations [44]. The metabolic changes that occur during pregnancy, including relative hyperglycemia, hyperlipidemia, and disturbance of coagulation, represent a transient excursion into the metabolic syndrome [45]. When imposed upon preexisting medical conditions such as chronic hypertension or diabetes mellitus, they are associated with a significant increased risk for adverse outcomes. The results of this investigation demonstrate this association, particularly among women whose fertility status declined from their first to their second pregnancy. The incidence of chronic hypertension was highest in both first and second pregnancies among women whose fertility status declined (3.4 and 2.9 %, respectively, for F-A and 2.9 and 3.8 %, respectively, for S-A). The incidence of diabetes mellitus was also the highest among the S-A group (3.8 %). Fertile women whose fertility status declined showed the largest increases in gestational diabetes between their first and second pregnancies (2.8 to 6.8 % for F-S and 3.7 to 7.4 % for F-A). In first births, the preterm birth rate was the highest among ART births (9.8 % for A-S and 10.0 % for A-A births) but also elevated above the national average (7.74 % in 2014) [46] for women whose fertility status would decline in their second birth (10.0 % for F-S and 8.6 % for S-A births). These findings support the recommendation that women with adverse pregnancy outcomes be monitored more closely after delivery for the development of cardiovascular and metabolic disease [45, 47–53]. As the risk for adverse outcomes is substantially higher for ART pregnancies, these women should also be included in this group at greater risk for future disease.

Strengths and limitations

The MOSART study, which includes linking ART cycles to the vital records and hospital utilization data, represents the first time these datasets have been linked using direct identifiers from both datasets. ART national surveillance summaries are limited to birth outcomes reported by the patient herself or her obstetric provider [54–56]. Prior studies [44, 45] have relied on linkages between ART cycles and vital records using only maternal and infant dates of birth or probabilistic algorithms [56]. Although there is a high degree of comparability between the SART CORS and vital records [27], our study design assures more accurate linkage between ART treatment cycles, vital records, and the hospital discharge birth data and a more complete picture of perinatal outcomes. Although this study has several unique advantages over prior ART research, it is also subject to a number of limitations. This study uses retrospective data from several centralized datasets, and although this is advantageous to achieve large numbers, we had the disadvantage that data entered into the SART CORS system is not as rigorously controlled as data collected for a prospective research study. Likewise, the primary purpose of vital records is civil registration, with public health research and surveillance being secondary uses. One of the limitations

of comparing our results to the published literature is that the latter is often based on data spanning decades, during which time both ART procedures and outcomes have improved. Another limitation of this analysis is that it only includes women in Massachusetts. There may be demographic and other differences in patients in other regions of the country and with other healthcare systems, potentially limiting the generalizability of our findings. Future analyses are planned to evaluate the health status of women by body mass index, which was recently added to the Massachusetts birth certificate, as well as by fetal loss. There are also plans to track the future health of the women in this cohort to evaluate their risks for cardiovascular and metabolic diseases.

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Compliance with ethical standards

Conflict of interest Barbara Luke is a research consultant to the Society for Assisted Reproductive Technology; all other authors report no conflict of interest.

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