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ASSISTED REPRODUCTION TECHNOLOGIES

Sex differences in infant health following ART-treated, subfertile, and fertile deliveries

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Abstract

Purpose Among infants following ART-treated, subfertile, and fertile deliveries to determine (1) the presence and magnitude of sex differences in health outcomes and (2) whether the presence of sex differences varied among maternal fertility groups.

Methods Retrospective cohort analysis of infants born in Massachusetts (MA) in 2004–2013 who were conceived by ART. The Society for Assisted Reproductive Technology Clinic Outcome Reporting System was linked to the Pregnancy to Early Life Longitudinal data system, which links birth certificates to hospital discharge records for MA mothers and infants. Included were singletons born via ART-treated, subfertile, and fertile deliveries. Multivariable logistic regression was used to model the association between infant sex and health outcomes, controlling for maternal demographic and health characteristics.

Results A total of 16,034 ART-treated, 13,277 subfertile, and 620,375 fertile singleton live births were included. For all three groups, males had greater odds of being preterm (AOR range 1.15–1.2), having birth defects (AOR range 1.31–1.71), experiencing respiratory (AOR range 1.33–1.35) and neurologic (AOR range 1.24–1.3) conditions, and prolonged hospital stay (AOR range 1.19–1.25) compared to females. The interaction between maternal fertility group and infant sex for all infant outcomes was nonsignificant, denoting that the presence of sex differences among fertile, subfertile, and ART groups did not vary.

Conclusion Sex differences in birth outcomes of infants following ART-treated, subfertile, and fertile deliveries exist but the magnitude of these differences does not vary among these maternal fertility groups.

Keywords Sex differences · Assisted reproductive technology · Infant health

Abbreviations

ART	Assisted reproductive technology
GA	Gestational age
MOSART	Massachusetts Outcome Study of Assisted Reproductive Technology
PELL	Pregnancy to Early Life Longitudinal
S A R T CORS	Society for Assisted Reproductive Technology Clinic Outcome Reporting System

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Introduction

Sex differences in health outcomes among pediatric and adult populations exist. Among infants, the recently growing body of literature has demonstrated sex differences in prematurity, birthweight, respiratory morbidity, congenital malformations, and mortality. Using animal models, investigators have identified some biologic mechanisms that underlie observed sex differences in overall fetal growth, specific organ development, and response to varying hormonal environments [1–6]. The use of assisted reproductive technology (ART)—treatments involving removal of eggs from a woman's ovary and manipulation of these in vitro—has increased dramatically with nearly 77,000

babies born in the USA by ART in 2016 [7]. Basic science and population-based epidemiologic studies focused on sex differences, to date, have considered infants born from fertile and ART deliveries as one homogenous group. Given the various medical and surgical interventions required in ART treatment and their potential impact on fetal development, it is critical to understand whether the trends in sex differences in infant health that are observed in the general population are also present, or even exacerbated, in infants delivered after ART treatment. It is well-established that infants born after ART are at higher risk for preterm birth, low birthweight, and various organ system morbidities including those of the respiratory, infectious disease, and neurologic systems [8–10]. However, data are lacking on whether the incidence of these adverse outcomes varies by infant sex and whether the direction and magnitude of these sex differences are different than in infants born after fertile deliveries or deliveries to women with subfertility but no ART treatment. Consideration of sex differences in neonatal outcomes has been shown to be important in understanding risk profiles for adverse birth outcomes, particularly for preterm infants. At a population-level, male fetal sex confers greater risk for mortality and morbidities among extremely preterm infants [11, 12]. However, this risk by fetal sex has not been stratified by maternal fertility status. To address this knowledge deficit, the objectives of this study are to determine (1) the presence and magnitude of sex differences in health outcomes among infants following ART-treated, subfertile, and fertile deliveries and (2) whether the presence of sex differences varies among infants following ART-treated, subfertile, and fertile deliveries.

Patients and methods

Data sources

Data were obtained from the Massachusetts Outcome Study of Assisted Reproductive Technology (MOSART) database, which includes data from (1) the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) database, containing cycle-based ART data from the majority of US ART clinics, and (2) the Pregnancy to Early Life Longitudinal (PELL) data system, an ongoing population-based system that includes birth certificates, death records, and hospital utilization data for Massachusetts resident mothers and infants. Institutional Review Board approval was obtained from the Massachusetts Department of Public Health and Dartmouth-Hitchcock Health. The SART Research Committee approved the study.

The SART CORS contains comprehensive data from over 90% of US ART clinics. Data were 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 demographics, ART diagnoses, treatment parameters, and pregnancy outcomes. One hundred percent of Massachusetts clinics report data to SART CORS.

The PELL data system has linked information on more than 99% of all births and fetal deaths in Massachusetts since 1998 to hospital utilization data for women and their children. Birth defects data are linked from the Massachusetts Birth Defects Monitoring Program (BDMP). BDMP conducts population-based active surveillance of structural birth defects among Massachusetts residents diagnosed through 1 year of age through analysis of data from delivery and specialty care hospitals, birthing centers, and vital records.

The MOSART database links the SART CORS and PELL data systems for all children born in Massachusetts hospitals to Massachusetts resident women between July 1, 2004, and December 31, 2013. 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 data from both SART and PELL when this analysis was initiated. A deterministic five-phase linkage algorithm was implemented with matching based on the baby's date of birth, mother's date of birth, mother's first name and last name, and father/partner's last name [13]. The linkage rate was 90.2% overall and 94.6% for deliveries in which both mother's zip code and clinic were in Massachusetts.

Cohort selection

Inclusion criteria were as follows: (1) mothers' first delivery in MOSART, regardless of parity, so as to not evaluate multiple deliveries to a single woman; (2) singleton gestation; (3) maternal age ≥ 18 years; (4) live birth; (5) infants with inpatient birth hospital records.

Outcomes

Using ICD-9 codes from birth hospitalization records and birth certificates, the following infant health outcomes were assessed: preterm birth (< 37 weeks), small for gestational age (SGA), low birth weight (LBW; < 2500 g), neonatal mortality during birth hospitalization (death between day of delivery and the last day of hospitalization), prolonged hospital stay (for infants ≥ 35 weeks GA, > 3 days for infants born vaginally, and > 5 days for those born by cesarean section). The outcome of birth defects, obtained from the BDMP such as various congenital heart malformations and facial anomalies such as cleft lip and palate, was categorized as chromosomal or non-chromosomal according to criteria in a previously published MOSART study [14, 15]. Infants transferred to higher levels of care after birth were included. Specific conditions by

the following systems were also assessed: infectious disease, cardiovascular, respiratory, gastrointestinal/nutrition, neurologic, and hematologic (ICD-9 codes shown in Appendix 1). Length of gestation was calculated based on clinical estimates by first trimester ultrasound and when those were missing the estimated date of last menstrual period. Birthweight *z*-scores were calculated to evaluate adequacy of weight-for-age using Massachusetts population-based standards and modeled as continuous and categorical variables. We generated sex-, race/ethnicity-, and gestation-specific birthweight means and standard deviations using Massachusetts data for live births from 2004 to 2010. Infants with *z*-scores of ≤ 1.28 (below the 10th percentile for gestation) were classified as SGA.

Primary exposure and delivery classification

Infant sex was the primary exposure and these data were obtained from birth certificate records.

Maternal fertility groups were categorized as fertile, subfertile, or ART-treated. Women were classified as ART-treated if the delivery was linked to ART data from the SART CORS online database. As defined in the article by Zegers-Hochschild et al., ART only includes those procedures that include retrieval of oocytes and in vitro manipulation of oocytes and embryos. IUI, administration of gonadotropins, and other procedures are not included [16]. Women were classified as "subfertile" if they had either a diagnosis of infertility (ICD-9 codes 628 and V230) on the index or prior hospitalization record or indication on the birth or fetal death certificate of use of non-ART medically assisted reproduction (MAR) for index or prior deliveries [17]. The term subfertility was used rather than infertility or MAR [18] to indicate that this was a combination measure rather than one or the other of these determinations. Women who had undergone ART in prior pregnancies during or preceding the MOSART study period were also defined as subfertile for the index pregnancy. Fertile women were those in neither the ART-treated nor the subfertile groups.

Additional independent variables included maternal age, race/ethnicity, education, marital status, parity, insurance status, chronic and pregnancy-induced hypertension, non-gestational and gestational diabetes, and year of birth.

Statistical methods

To address aim 1, we compared birth outcomes by sex of infants born to ART-treated, subfertile, and fertile mothers using the chi-square statistics (alpha = 0.05). Logistic regression modeling was performed to assess the independent association between infant sex and adverse birth outcomes, controlling for maternal age, race/ethnicity, education, insurance status at birth, pre-existing diabetes, pre-existing hypertension, pregnancy-induced hypertension, gestational diabetes, parity, and birth year. Given the higher risk of adverse health outcomes in younger GA infants, we also controlled for GA in all adjusted models except those that assessed preterm birth as the outcome. For the outcome of prolonged infant hospital stay among infants born ≥ 35 weeks GA, we also adjusted for maternal length of hospital stay. To address aim 2, we assessed the interaction of infant sex and maternal fertility groups for all infant outcomes to determine whether the presence of sex differences varied across maternal fertility groups. Likelihood ratio test was used to compare the models with and without the interaction term, and the Wald test was used to assess the interaction term. Results, presented as adjusted odds ratios (AORs) and 95% confidence intervals (95% CIs), were considered significant with p values < 0.05 for bivariate analyses, and when the 95% CIs did not include 1. All analyses were performed using the SAS software, version 9.3 (SAS Institute, Cary, NC).

Results

Cohort

Our study cohort included 649,686 infants with 620,375 fertile, 13,277 subfertile, and 16,034 ART-infants. For female and male infants across fertility groups, there were no statistically significant differences in maternal age, race/ethnicity, education, insurance, chronic and pregnancy-induced hypertension, and non-gestational diabetes (Table 1). Among infants born to fertile women, female infants were more likely to be born to mothers with 3 or more prior births, whereas in the subfertile group, male infants were more likely to be born to mothers with 3 or more prior births. There was no sex difference in the ART-treated group with regard to prior births. In the fertile and subfertile groups, male infants were more likely to be born to mothers with gestational diabetes compared to female infants while there was no difference in the ART group.

Bivariate analysis results

There were significant sex differences in several health outcomes among infants born to ART-treated, subfertile, and fertile women (Table 2). Male infants were more likely to be born at younger gestational ages, have non-chromosomal birth defects, and have conditions of the respiratory and neurologic systems compared to female infants. In addition, for infants ≥ 35 weeks, male infants were more likely to have prolonged hospital stays across all three groups. For infants born to fertile

Table 1 Maternal cohort characteristics

Demographic characteristic	Category	Fertile			Subfertile			ART		
		Female, %	Male, %	*p* value	Female, %	Male, %	*p* value	Female, %	Male, %	*p* value
Total *N*		302771	317604		6552	6725		7737	8297	
Age	18–29	47.2	47.2	0.6602	12.8	11.6	0.2274	7.7	7.6	0.6322
	30–34	31.9	31.9		34.6	34.7		31.8	32.1	
	35–37	12.7	12.6		24.9	25.3		24.1	25	
	38–40	6.1	6.1		17.9	18		20	19.9	
	41–42	1.6	1.5		6.7	6.7		8.9	8.5	
	43+	0.6	0.6		3.2	3.7		7.4	6.9	
Race/ethnicity	Hispanic	15.6	15.6	0.1762	5.4	5.8	0.4311	4.3	4.2	0.9336
	Non-Hispanic White	65.3	65.2		82.6	81.7		82.8	82.8	
	Non-Hispanic Black	9.3	9.3		3.6	3.6		3.4	3.6	
	Asian/Pacific Island	9.8	9.9		8.4	8.9		9.4	9.4	
Education	< HS or HS/GED	44.5	44.2	0.1708	16.4	16.3	0.8866	12.6	12.4	0.4735
	Some college	13.6	13.7		12.8	12.5		11.4	10.9	
	College+	41.9	42.1		70.8	71.2		76	76.7	
Parity	1	45	45	0.0578	37.9	39.3	0.0057*	62.4	63.7	0.154
	2	34.5	34.7		40.9	38.1		30.5	29.1	
	3+	20.6	20.3		21.3	22.6		7.1	7.2	
Chronic hypertension	No	98.2	98.3	0.1865	97.6	97.4	0.4822	97	97.1	0.6532
	Yes	1.8	1.7		2.4	2.6		3	2.9	
Pregnancy-induced hypertension	No	91.2	91.2	0.928	89.5	89.3	0.6583	87	87.1	0.8988
	Yes	8.8	8.8		10.5	10.7		13	12.9	
Non-gestational diabetes	No	98.8	98.8	0.7086	98.4	98.4	0.7938	98.2	98.3	0.7296
	Yes	1.2	1.2		1.6	1.6		1.8	1.7	
Gestational diabetes	No	94	93.8	0.0016*	91.3	90	0.0082*	91.3	91.8	0.254
	Yes	6	6.2		8.7	10		8.7	8.2	
Prolonged length of hospital stay for mothers	No	96.2	96.2	0.8268	96.4	96.3	0.8273	94.6	94.8	0.5304
	Yes	3.8	3.8		3.6	3.7		5.4	5.2	
Year of birth	2004	5.6	5.5	0.983	5.6	5.3	0.3795	3	2.5	0.0003*
	2005	10.8	10.9		8.5	8.7		10.1	8.7	
	2006	10.9	10.9		9.7	9.5		9.9	9.4	
	2007	11	11		9.4	9.7		9.7	10.3	
	2008	10.9	10.8		9.7	9.7		9.4	10	
	2009	10.4	10.5		8.8	9.8		10.1	10.7	
	2010	10.1	10.1		9.1	9.4		12.2	11.7	
	2011	10.2	10.2		12	11.4		10.3	11.5	
	2012	10.1	10.1		12.7	13.4		12.4	11.3	
	2013	10	9.9		14.3	13.1		12.9	13.9	
Insurance at delivery	Private	55.7	55.9	0.3426	86.7	87.3	0.1107	93.3	93.8	0.2197
	Public	44.3	44.1		13.3	12.6		6.7	6.2	

*Due to rounding of prevalence estimates, percentages in some categories of maternal characteristics may not add to 100%

mothers, male infants were less likely to be of low birthweight and have infectious disease and gastrointestinal/nutritional and hematologic conditions compared to females. This pattern attenuated among infants born to subfertile mothers or those with ART treatment.

Multivariable analysis results

For each outcome, female infants serve as the reference group. For infants born to ART-treated, subfertile, and fertile mothers, male infants were more likely to be born preterm,

Table 2 Infant outcomes by maternal fertility group and infant sex

Infant outcomes	Category	Fertile			Subfertile			ART		
		Female, %	Male, %	*p* value	Female, %	Male, %	*p* value	Female, %	Male, %	*p* value
Total *N*		302771	317604		6552	6725		7737	8297	
Gestational age	≤ 27 weeks	0.3	0.4	< 0.0001*	0.5	0.5	0.0016*	0.5	0.6	0.0015*
	28–33 weeks	1.1	1.3		1.2	1.9		2.1	2.6	
	34–36 weeks	4.3	4.9		5.3	5.8		6.7	7.8	
	37–38 weeks	20.5	21.5		23.1	24.6		23.2	24.3	
	39+ weeks	73.7	72		69.9	67.2		67.5	64.8	
Birthweight	≤ 1000 g	0.4	0.4	< 0.0001*	0.7	0.5	0.4133	0.7	0.7	0.0907
	1001–1500 g	0.4	0.4		0.4	0.6		0.7	1	
	1501–2500 g	5.0%	4.1		4.7	4.6		6.8	6	
	2501+ g	94.2	95.1		94.2	94.4		91.9	92.4	
Small for gestational age	No	92.1	92.1	0.7809	93.5	94.1	0.1839	92	92.3	0.6044
	Yes	7.9	7.9		6.5	5.9		8	7.7	
LGA	No	90.2	90.5	0.0056*	88.7	89.1	0.5496	90.5	90.4	0.9074
	Yes	9.8	9.5		11.3	10.9		9.5	9.6	
Preterm birth (< 37 weeks)	No	94.1	93.3	< 0.0001*	92.8	91.5	0.0056*	90.4	88.9	0.0012*
	Yes	5.9	6.7		7.2	8.5		9.6	11.1	
Low birthweight (< 2500 g)	No	94.2	95.1	< 0.0001*	94.2	94.4	0.6296	91.9	92.4	0.2175
	Yes	5.8	4.9		5.8	5.6		8.1	7.6	
Neonatal mortality	No	99.8	99.8	0.0184*	99.7	99.7	0.6897	99.8	99.8	0.7785
	Yes	0.2	0.2		0.3	0.3		0.2	0.2	
Birth defects	No	98.6	98	< 0.0001*	98.5	97.4	<0.0001*	98.2	97.6	0.0135*
	Yes	1.4	2		1.5	2.6		1.8	2.4	
Chromosomal birth defects	No	99.7	99.7	0.1471	99.5	99.5	0.5259	99.6	99.6	0.8899
	Yes	0.3	0.3		0.5	0.5		0.4	0.4	
Non-chromosomal birth defects	No	98.9	98.3	< 0.0001*	98.9	98	<0.0001*	98.5	98	0.0055*
	Yes	1.1	1.7		1.1	2		1.5	2	
Infectious disease conditions	No	99	98.8	< 0.0001*	98.9	98.9	0.8097	98.7	98.5	0.2886
	Yes	1	1.2		1.1	1.1		1.3	1.5	
Respiratory conditions	No	92.8	90.5	< 0.0001*	91	88	< 0.0001*	89.5	86	< 0.0001*
	Yes	7.2	9.5		9	12		10.5	14	
Gastrointestinal/nutritional conditions	No	97.5	97.2	< 0.0001*	96.9	96.3	0.0601	95.5	95	0.0997
	Yes	2.5	2.8		3.1	3.7		4.5	5	
Neurologic conditions	No	97.2	96.3	< 0.0001*	97.4	96.7	0.0213*	96.9	96	0.0025*
	Yes	2.8	3.7		2.6	3.3		3.1	4	
Hematologic conditions	No	96.3	96	< 0.0001*	95.5	95.8	0.3378	94.9	95	0.712
	Yes	3.7	4		4.5	4.2		5.1	5	
Prolonged hospital stay for infants	No	95.3	94.5	< 0.0001*	95.7	94.6	0.0067*	94.9	93.7	0.0013*
	Yes	4.7	5.5		4.3	5.4		5.1	6.3	

have non-chromosomal birth defects, have respiratory and neurologic conditions, and, for infants ≥ 35 weeks gestational age, have prolonged hospital stays but were less likely to be born of low birthweight. For male infants born to fertile mothers, they were more likely to have infectious disease and hematologic and gastrointestinal/nutritional conditions (Table 3).

Interaction of infant sex and maternal fertility group

For all infant outcomes, there was no significant interaction by sex and maternal fertility group, indicating that, while sex differences may exist, the magnitude of sex differences across ART-treated, subfertile, and fertile groups did not vary (Table 4).

Table 3 Adjusted models for infant outcomes by fertility group and infant sex

Outcomes	Category	Fertile			Subfertile			ART		
		OR	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
Preterm birth (< 37 weeks)‡	Females	1	Reference		1	Reference		1	Reference	
	Males	1.15	1.13, 1.17	< 0.0001	1.18	1.04, 1.35	0.0115	1.2	1.08, 1.33	0.0007
LGA‡	Females	1	Reference		1	Reference		1	Reference	
	Males	0.98	0.96, 0.99	0.0093	0.94	0.84, 1.05	0.257	1.02	0.92, 1.14	0.6871
Small for gestational age‡	Females	1	Reference		1	Reference		1	Reference	
	Males	1	0.99, 1.02	0.6162	0.9	0.77, 1.04	0.1499	0.98	0.87, 1.1	0.7143
Low birthweight (< 2500 g)	Females	1	Reference		1	Reference		1	Reference	
	Males	0.6	0.59, 0.62	< 0.0001	0.67	0.54, 0.83	0.0002	0.68	0.58, 0.81	< 0.0001
Neonatal mortality	Females	1	Reference		1	Reference		1	Reference	
	Males	1.06	0.95, 1.19	0.2907	0.78	0.43, 1.42	0.4246	1.08	0.52, 2.24	0.8308
Birth defects	Females	1	Reference		1	Reference		1	Reference	
	Males	1.46	1.4, 1.52	< 0.0001	1.71	1.33, 2.2	< 0.0001	1.31	1.05, 1.63	0.0165
Chromosomal birth defects	Females	1	Reference		1	Reference		1	Reference	
	Males	1.08	0.98, 1.19	0.1361	1.14	0.71, 1.86	0.5851	0.95	0.56, 1.61	0.8547
Non-chromosomal birth defects	Females	1	Reference		1	Reference		1	Reference	
	Males	1.55	1.48, 1.61	< 0.0001	1.95	1.46, 2.62	< 0.0001	1.39	1.09, 1.77	0.0076
Infectious disease conditions	Females	1	Reference		1	Reference		1	Reference	
	Males	1.15	1.09, 1.21	< 0.0001	0.88	0.62, 1.24	0.4659	1.11	0.85, 1.46	0.4484
Hematologic conditions	Females	1	Reference		1	Reference		1	Reference	
	Males	1.07	1.04, 1.10	< 0.0001	0.91	0.77, 1.08	0.2779	0.95	0.82, 1.09	0.4435
Cardiovascular conditions*	Females	1	Reference		1	Reference		1	Reference	
	Males	--	--	--	--	--	--	--	--	--
Respiratory conditions	Females	1	Reference		1	Reference		1	Reference	
	Males	1.34	1.32, 1.37	< 0.0001	1.33	1.18, 1.49	< 0.0001	1.35	1.23, 1.49	< 0.0001
Gastrointestinal/nutritional conditions	Females	1	Reference		1	Reference		1	Reference	
	Males	1.07	1.03, 1.10	< 0.0001	1.15	0.95, 1.4	0.1426	1.08	0.93, 1.25	0.3067
Neurologic conditions	Females	1	Reference		1	Reference		1	Reference	
	Males	1.3	1.26, 1.33	< 0.0001	1.24	1.01, 1.53	0.0378	1.29	1.09, 1.54	0.0033
Prolonged hospital stay for infants†	Females	1	Reference		1	Reference		1	Reference	
	Males	1.19	1.16, 1.21	< 0.0001	1.2	1.02, 1.42	0.0267	1.25	1.08, 1.43	0.0019

† All models are adjusted for mother's age, race, education, insurance at delivery, parity, gender, gestational age (continuous), any hypertension (combined measure chronic and gestational hypertension), any diabetes (combined measure chronic and gestational diabetes), and year of birth

‡ Models for preterm birth, LGA, and SGA are adjusted for mother's age, race, education, insurance at delivery, parity, gender, any hypertension (combined measure chronic and gestational hypertension), any diabetes (combined measure chronic and gestational diabetes), and year of birth

*Due to limited number of affected infants, these models resulted in non-convergence

Discussion

In this population-based analysis of sex differences in health outcomes of infants born to ART-treated, subfertile, and fertile mothers, we found that, after adjusting for key maternal and infant characteristics, sex differences in birth outcomes exist for all groups.

To our knowledge, with the exception of birthweight, very few studies of health outcomes of infants born to ART-treated women have considered infant sex as the main exposure [19, 20]. In their study of the effects on embryo culture media on birthweight of singletons, Gu et al. demonstrated that, while culture media did not independently impact birthweight, infant gender was founded to be significantly related to neonatal birthweight in their multivariable analysis with males being heavier than females [19]. However, as in prior studies, infant sex was considered a covariate and not the primary exposure in the relationship between culture media and birthweight. Sex differences in infant outcomes after ART can perhaps be extrapolated from cohort descriptions of studies such as the

Table 4 Interaction by infant sex and maternal fertility group

	Without GA *p* value	With GA *p* value
Preterm birth (< 37 weeks)	0.7557	
Small for gestational age	0.3182	0.3375
Low birthweight (< 2500 g)	0.0354	0.1425
Neonatal mortality	0.6667	0.5834
Birth defects	0.2826	0.2858
Chromosomal birth defects	0.8671	0.865
Non-chromosomal birth defects	0.2074	0.2094
Respiratory conditions	0.8958	0.9256
Neurologic conditions	0.8987	0.8964
Prolonged hospital stay for infants	0.7208	0.7
IUGR	0.929	0.8938

recently published investigation of infant and late childhood mortality among children conceived naturally or by ART [20]. Rodriguez-Wallberg et al. show that, among naturally conceived children, males have higher mortality than females while there appears to be no difference in the ART-conceived children. However, this extrapolation is based upon overlapping versus non-overlapping confidence intervals around their crude mortality rate estimates without consideration of other confounders.

Given the lack of statistically significant interaction across fertility groups in our analysis, our study demonstrates that the presence of sex differences in the ART group does not differ between fertile and subfertile groups. For the general population, there is a growing body of literature highlighting sex differences in fetal growth and infant health outcomes. Sex-specific placental responses in fetal development, particularly related to fetal programming and epigenetic differences, have been shown in several studies [21–25]. Moreover, following birth, prior work has shown that sex differences exist in several health outcomes among the preterm population, such as brain volume, respiratory distress syndrome, and mortality [2–5, 26]. However, these analyses do not account for mode of conception and thus, it is not clear if these findings are uniform across infants born to women of varying fertility group.

While our study demonstrated that the presence of sex differences in infant outcomes did not vary across fertility groups, we are unable to determine whether the mechanisms by which these differences are expressed in the fertile, subfertile, and ART groups are similar. We hypothesize that, for the ART group, the complex manipulations and interventions involved in embryo development, storage, and implantation, in addition to the medically altered maternal hormonal milieu, may impact fetal growth and organ development in a sex-specific manner that may be mechanistically different than in the fertile and subfertile groups. While this study is one of the first to determine sex differences in infant outcomes among ART-treated mothers, prior work has shown differences in the secondary sex ratio among infants born to mothers after ART treatment versus natural conception. Supramaniam et al. and Dean et al. reported that ICSI increased female births while IVF increased male births [24, 25]. Luke et al. found that the use of ICSI with blastocyst-stage embryos was associated with a decrease in the sex ratio of male infants [26].

There are several limitations to our work. First, the MOSART database is comprised of vital statistics and hospital-level administrative discharge codes, and thus, some parameters, such as maternal and paternal body mass index (BMI), were not available. We also recognize that, despite our best attempts to control for differences in maternal characteristics across fertility groups, residual confounding may still persist. Data related to pregnancy course such as fetal growth and utero-placental Doppler ultrasound data were not available and thus, it is now known when sex differences in fetal/infant outcomes first became apparent. Data on paternal health including infertility and BMI were also unavailable. Finally, findings may not be generalizable since our cohort included only Massachusetts resident births. Moreover, as is the case with population-based observational studies, in general, while we demonstrate significant sex difference in health outcomes among infants conceived by ART, we are unable to identify the mechanisms by which these differences come about.

Despite these limitations, this population-based study is the first, to our knowledge, to investigate sex differences in infant outcomes after ART. We find that, after adjusting for key maternal and infant characteristics, sex differences in birth outcomes do exist for infants born to women after ART but are also present in infants born to fertile and subfertile women. Moreover, while sex differences for some health outcomes are similar across fertility groups, others do vary. Future studies should consider infant sex as an independent biologic variable when assessing the relationship between receipt of ART and child health outcomes.

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Data availability Access to data may be limited due to restrictions placed by the Massachusetts Department of Public Health.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Code availability Access to software application or custom code may be limited due to restrictions placed by the Massachusetts Department of Public Health.

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