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The risk of birth defects with conception by ART

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STUDY QUESTION: What is the association between ART conception and treatment parameters and the risk of birth defects?

SUMMARY ANSWER: Compared to naturally conceived singleton infants, the risk of a major nonchromosomal defect among ART singletons conceived with autologous oocytes and fresh embryos without use of ICSI was increased by 18%, with increases of 42% and 30% for use of ICSI with and without male factor diagnosis, respectively.

WHAT IS KNOWN ALREADY: Prior studies have indicated that infertility and ART are associated with an increased risk of birth defects but have been limited by small sample size and inadequate statistical power, failure to differentiate results by plurality, differences in birth defect definitions and methods of ascertainment, lack of information on ART treatment parameters or study periods spanning decades resulting in a substantial historical bias as ART techniques have improved.

STUDY DESIGN, SIZE, DURATION: This was a population-based cohort study linking ART cycles reported to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) from 1 January 2004 to 31 December 2015 that resulted in live births from 1 September 2004 to 31 December 2016 in Massachusetts and North Carolina and from 1 September 2004 to 31 December 2015 for Texas and New York: these were large and ethnically diverse States, with birth defect registries utilizing the same case definitions and data collected, and with high numbers of ART births annually. A 10:1 sample of non-ART births were chosen within the same time period as the ART birth. Naturally conceived ART siblings were identified through the mother's information. Non-ART children were classified as being born to women who conceived with ovulation induction (OI)/IUI when there was an indication of infertility treatment on the birth certificate, but the woman did not link to the SART CORS; all others were classified as being naturally conceived.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study population included 135 051 ART children (78 362 singletons and 56 689 twins), 23 647 naturally conceived ART siblings (22 301 singletons and 1346 twins) and 9396 children born to women treated with OI/IUI (6597 singletons and 2799 twins) and 1 067 922 naturally conceived children (1 037 757 singletons and 30 165 twins). All study children were linked to their respective State birth defect registries to identify major defects diagnosed within the first year of life. We classified children with major defects as either chromosomal (i.e. presence of a chromosomal defect with or without any other major defect) or nonchromosomal (i.e. presence of a major defect but having no chromosomal defect), or all major defects (chromosomal and nonchromosomal). Logistic regression models were used to generate adjusted odds ratios (AORs) and 95% CI to evaluate the risk of birth defects

due to conception with ART (using autologous oocytes and fresh embryos), and with and without the use of ICSI in the absence or presence of male factor infertility, with naturally conceived children as the reference. Analyses within the ART group were stratified by combinations of oocyte source (autologous, donor) and embryo state (fresh, thawed), with births from autologous oocytes and fresh embryos as the reference. Analyses limited to fresh embryos were stratified by oocyte source (autologous, donor) and the use of ICSI. Triplets and higher-order multiples were excluded.

MAIN RESULTS AND THE ROLE OF CHANCE: A total of 21 998 singleton children (1.9%) and 3037 twin children (3.3%) had a major birth defect. Compared to naturally conceived children, ART singletons (conceived from autologous oocytes, fresh embryos without the use of ICSI) had increased risks of a major nonchromosomal birth defect (AOR 1.18, 95% 1.05, 1.32), cardiovascular defects (AOR 1.20, 95% CI 1.03, 1.40), and any birth defect (AOR 1.18, 95% CI 1.09, 1.27). Compared to naturally conceived children, ART singletons conceived (from autologous oocytes, fresh embryos) with the use of ICSI, the risks were increased for a major nonchromosomal birth defect (AOR 1.30, 95% CI 1.16, 1.45 without male factor diagnosis; AOR 1.42, 95% CI 1.28, 1.57 with male factor diagnosis); blastogenesis defects (AOR 1.49, 95% CI 1.08, 2.05 without male factor; AOR 1.56, 95% CI 1.17, 2.08 with male factor); cardiovascular defects (AOR 1.28, 95% CI 1.10,1.48 without male factor; AOR 1.45, 95% CI 1.27, 1.66 with male factor); in addition, the risk for musculoskeletal defects was increased (AOR 1.34, 95% CI 1.01, 1.78 without male factor) and the risk for genitourinary defects in male infants was increased (AOR 1.33, 95% CI 1.08, 1.65 with male factor). Comparisons within ART singleton births conceived from autologous oocytes and fresh embryos indicated that the use of ICSI was associated with increased risks of a major nonchromosomal birth defect (AOR 1.18, 95% CI 1.03, 1.35), blastogenesis defects (AOR 1.65, 95% CI 1.08, 2.51), gastrointestinal defects (AOR 2.21, 95% CI 1.28, 3.82) and any defect (AOR 1.11, 95% CI 1.01, 1.22). Compared to naturally conceived children, ART singleton siblings had increased risks of musculoskeletal defects (AOR 1.32, 95% CI 1.04, 1.67) and any defect (AOR 1.15, 95% CI 1.08, 1.23). ART twins (conceived with autologous oocytes, fresh embryos, without ICSI) were at increased risk of chromosomal defects (AOR 1.89, 95% CI 1.10, 3.24) and ART twin siblings were at increased risk of any defect (AOR 1.26, 95% CI 1.01, 1.57). The 18% increased risk of a major nonchromosomal birth defect in singleton infants conceived with ART without ICSI (~36% of ART births), the 30% increased risk with ICSI without male factor (~33% of ART births), and the 42% increased risk with ICSI and male factor (~31% of ART births) translates into an estimated excess of 386 major birth defects among the 68 908 singleton children born by ART in 2017.

LIMITATIONS, REASONS FOR CAUTION: In the SART CORS database, it was not possible to differentiate method of embryo freezing (slow freezing vs vitrification), and data on ICSI was only available in the fresh embryo ART group. In the OI/IUI group, it was not possible to differentiate type of non-ART treatment utilized, and in both the ART and OI/IUI groups, data were unavailable on duration of infertility.

WIDER IMPLICATIONS OF THE FINDINGS: The use of ART is associated with increased risks of a major nonchromosomal birth defect, cardiovascular defect and any defect in singleton children, and chromosomal defects in twins; the use of ICSI further increases this risk, the most with male factor infertility. These findings support the judicious use of ICSI only when medically indicated. The relative contribution of ART treatment parameters versus the biology of the subfertile couple to this increased risk remains unclear and warrants further study.

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Introduction

ART includes all interventions involving the *in vitro* handling of both human oocytes and sperm or of embryos for the purpose of reproduction. This includes, but is not limited to, IVF and embryo transfer, gamete intra-Fallopian transfer, zygote intra-Fallopian transfer, gamete and embryo cryopreservation, oocyte and embryo donation, and gestational carrier cycles (Zeger-Hochschild *et al.*, 2017). ART-conceived children accounted for 2% of all births in the USA in 2017, a proportion which has more than doubled since 2000 (Martin *et al.*, 2002, 2018; Toner *et al.*, 2016; Centers for Disease Control and Prevention, 2019). It is well established that infertility is associated with compromised maternal and infant outcomes, including higher risks for birth defects (Hansen *et al.*, 2002, 2012; Halliday *et al.*, 2010; Davies *et al.*, 2012a). An unresolved issue in ART research is how much of this excess risk is due to the biology of the subfertile couple versus the treatments used to achieve a live birth (Edwards and Ludwig, 2003; Buck Louis *et al.*, 2005; Berntsen *et al.*, 2019). In the USA, birth defects are the leading cause of infant mortality, accounting for over 20% of infant deaths and one-third of all pediatric hospital admissions (Russo and Elixhauser, 2007; Ely and Driscoll, 2019). Some reports suggest that the rates of major birth defects are 30–40% higher after ART or ICSI or after conception by subfertile couples without treatment, compared to children conceived naturally (Hansen *et al.*, 2002, 2012, 2013; Halliday *et al.*, 2010; Davies *et al.*, 2012a). Many studies, though, are limited by their small sample size and inadequate statistical power, failure to differentiate results by plurality, differences in birth defect definitions and methods of ascertainment, lack of information

on ART treatment parameters or study periods spanning decades resulting in a substantial historical bias as ART techniques have improved (Källén *et al.*, 2005; Olson *et al.*, 2005; Schieve *et al.*, 2005; El-Chaar *et al.*, 2009; Welmerink *et al.*, 2010; Yan *et al.*, 2011; Seggers *et al.*, 2015; Han *et al.*, 2018). We report the results of the linkage of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) to birth certificates and birth defects registries of four US States to create the most contemporary population-based study in the USA of the association of ART with birth defects.

Materials and methods

This study linked data from birth certificates to data from birth defects registries and the national ART database, the SART CORS, in four States (New York, Texas, Massachusetts and North Carolina). Data from birth certificates (2004–2013) were collected in a study of the risk of childhood cancer and ART (Spector *et al.*, 2019). The remaining data were obtained in the current study of the risk of birth defects in ART. New York, Texas, Massachusetts and North Carolina were chosen for the current study because they are large and ethnically diverse, with birth defect registries utilizing the same case definitions and data collected. These four States ranked #2 #3, #6 and #12 in highest number of annual ART births in the USA, respectively, in 2016, accounting for 3.0%, 1.5%, 4.7% and 1.4% of all births in each State (Martin *et al.*, 2018; Sunderam *et al.*, 2019).

SART CORS data

The SART CORS contains comprehensive information on ART procedures from more than 83% of all clinics providing ART and more than 92% 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) (Centers for Disease Control and Prevention, 2019). The Society makes data available for research purposes to entities that have agreed to comply with SART research guidelines. Patients undergoing ART at SART member clinics sign clinical consent forms that include permission to use their data for research with appropriate provisions for safeguarding confidentiality. Data are submitted by individual clinics and verified by the medical director of each clinic. Approximately 10% of clinics are audited each year to validate the accuracy of reported data (Centers for Disease Control and Prevention, 2019). During each audit visit, data reported by the clinic are compared with information recorded in the medical record; most data fields have discrepancy rates less than 2%.

Fertility treatment data

ART represents only a small portion of all infertility treatments used in the USA. The National Survey of Family Growth reported that infertility services included medical advice (29%), infertility testing (27%), ovulation drugs (20%), artificial insemination (7.4%), surgery or treatment for blocked tubes (3.2%) and ART (3.1%) (Chandra *et al.*, 2014). Identifying non-ART treatments is challenging, as there is no national registry for these therapies. In the 2003 revision of the US Birth Certificate, a checkbox was added to indicate that the pregnancy resulted from infertility treatment (worded as: if yes, check all that apply): (i) *Fertility-enhancing drugs, artificial insemination or intrauterine insemination*; (ii) *Assisted reproductive technology (e.g. ART (in vitro fertilization), GIFT (gamete intrafallopian transfer))*. Of the four States in this study, Massachusetts has collected data on infertility treatment on its birth certificate since 1996 and adopted the other items in the 2003 revision in 2012; Texas adopted the revision in 2005; New York State in 2004, New York City in 2008 (New York City maintains a separate birth registry); and North Carolina in 2010. Births which linked to the SART CORS cycles were categorized as ART; births with an indication that they resulted from infertility treatment (via any infertility checkbox on the birth certificate) but that did not link to an ART cycle in the SART CORS were categorized as ovulation induction (OI)/IUI; the remaining births were categorized as naturally conceived. Since <1% of births were checked as OI/IUI, all births prior to implementation of the checkbox on each State's birth certificate were labeled as naturally conceived. We estimate that 7.8% of the naturally conceived births did not have the infertility checkboxes on their birth certificate during the study period. This nonresponse rate would have increased the number of OI/IUI births by 8.5%. However, only 41.8% of the ART-treated women had an infertility checkbox checked 'Yes,' indicating an under-response of 58.2% for the ART births. Assuming this would be true for the OI/IUI births as well, this would more than double the number of OI/IUI births.

Linkage procedure

This study linked ART cycles reported to the SART CORS from 1 January 2004 to 31 December 2015 that resulted in live births from 1 September 2004 to 31 December 2016 in Massachusetts and North Carolina and to 31 December 2015 in New York and Texas, to the birth certificates and birth defects registries in these four States. Initially, study States linked the SART CORS data to birth certificates. Each State received a SART CORS file with identifiers for women with ART cycles resulting in a live birth who were residents of that State during the study time period. The States linked the SART CORS data to birth certificate data to identify the ART-conceived births; >90% of the ART-conceived births were linked to their respective birth certificates. States then matched ART mothers to all study years to identify naturally conceived siblings of the ART birth reported to the SART CORS (ART siblings group); we did not include any ART siblings with an indication of infertility treatment on their birth certificates (OI/IUI). Any ART sibling who was conceived with ART was included in the ART group.

There were 97 582 ART-treated mothers of 158 698 children: 78 362 ART singletons and 22 301 ART singleton siblings, and 56 689 ART twins and 1346 ART twin siblings. Among the 97 582 ART-treated mothers, 61 327 had one ART singleton, 8247 had two ART singletons and 360 had three or more ART singletons; 27 675 had one set of ART twins and 173 had two sets of ART twins; 17 675 had one singleton sibling, 2014 had two singleton siblings, 193 had three or more singleton siblings and 698 had twin siblings.

For each delivery identified as having been conceived by ART, we requested that the subsequent 10 deliveries (all liveborn infants from a pregnancy) be selected as the non-ART comparison group, although not all States implemented this request, providing the next 10 births (individual children) instead. Each child was then linked to their

respective State's birth defects registry. The vital records/birth defects linked files were de-identified before being sent to the investigators. We then linked the de-identified files to ART treatment parameters from the SART CORS by the use of unique research identifiers to create the final analytic file. This study was approved by the Institutional Review Boards at Michigan State University, the University of Michigan, and each of the four study State Departments of Health. The Michigan State University IRB determined that this research did not involve human subjects, as defined in 45 CFR 46.102 (f), in review dated 13 November 2015.

Birth defects

The four States participating in this project are current or former Centers for Disease Control (CDC) Centers for Birth Defects Research and Prevention. As such, they conduct enhanced birth defects surveillance in terms of scope and quality of data. Each State conducts active or a combination of active and passive population-based surveillance that includes the major birth defects. These States employ standard case definitions, as defined by the National Birth Defects Prevention Study and National Birth Defects Prevention Network (NBDPN), and code birth defects using the CDC coding system adapted from British Pediatric Association codes, which is more specific for birth defects than ICD-9 or ICD-10 coding (Supplementary Table SI) (National Birth Defects Prevention Network (NBDPN), 2004). They employ multiple quality assurance procedures including validity checks, double-checking of assigned codes, clinical review of at least a subset of cases and comparison/verification between multiple data sources. They collect key demographic and clinical variables as defined by the NBDPN guidelines for conducting birth defects surveillance (www.NBDPN.org). For this study, we analyzed birth defects diagnosed within the first year of life, as defined in Supplementary Table SI. We then classified individuals with major birth defects as either 'chromosomal' (i.e. presence of a chromosomal defect with or without any other major defect) or 'nonchromosomal' (i.e. presence of a major defect but having no chromosomal defect). 'Any birth defect' is any ICD-9 code with the first 3 digits 740–759, and any ICD-10 code inclusive of Q00.0–07.9, 10–18.9, 20–28.9, 30–45.9, 50–56.4, 60–87.89 and 89–99.9.

Blastogenesis defects

We chose also to include birth defects classified as a group by Halliday *et al.* (2010) as blastogenesis defects, defined on the basis of pathologic development rather than by organ system. This allowed us to define defects which were expected to originate within the first 4 weeks of gestation, excluding cardiac defects. Disorders of blastogenesis in the current study were defined as the presence of one or more of the following: abdominal wall defects, vertebral segmentation defects, tracheoesophageal fistula, diaphragmatic defects, neural tube defects, anal atresia, renal agenesis, caudal regression sequence, laterality defects, sirenomelia, sacrococcyeal teratoma, holoprosencephaly, acro-renal field defect and ammelia, based on Halliday's grouping. Among children with a blastogenesis defect, 4% also had a chromosomal defect.

Groups

As described above, births were defined based on the presence or absence of subfertility/infertility and the method of conception. Births were categorized as natural-conceived, OI/IUI, ART, and natural-conceived ART siblings. The ART births were further divided into four subgroups depending on the combination of oocyte source (autologous or donor) and embryo state (fresh or thawed), based on our prior analyses indicating associations of these combinations with adverse perinatal outcomes (Luke *et al.*, 2019, 2020). From these subgroups, children born to ART-treated women from cycles using autologous oocytes and fresh embryos (AF) without the use of ICSI were physiologically most similar to fertile births. The reference group, natural-conceived births, were compared to OI/IUI births, ART siblings and children born to ART-treated women from AF cycles without ICSI, and children born to ART-treated women from AF cycles with ICSI with or without the diagnosis of male factor infertility. When comparing within the ART subgroups, the reference group was children born to ART-treated women from AF cycles, stratifying by the use of ICSI for fresh cycles (data on ICSI was not available for thawed embryos). When modeling ICSI (the injection of a single spermatozoon into an oocyte) and assisted hatching (perforating the zona pellucida to facilitate hatching of the embryo and subsequent implantation), we restricted the analysis to ART cycles that had the responses 'All' or 'None' for these two variables to avoid cycles in which some, but not all embryos were treated with these procedures.

Independent variables

Independent variables were selected *a priori* for inclusion in the models based on established associations with birth defects and/or ART. These included maternal age at delivery (grouped as 18–29, 30–34, 35–37, 38–40, 41–43 and $\geq$44 years), race (White, Black, American Indian/Alaskan Native, Asian/Pacific Islander, other or missing), Hispanic ethnicity, education (less than high school graduate, high school graduate or general educational development, some college or associate degree, bachelor's degree, post-graduate education or missing), parity (nulliparous, primiparous or multiparous prior to the index pregnancy), BMI (weight/height^2) ($\leq$24, underweight or normal weight; 25–29, overweight, and $\geq$30, obese, or missing) calculated from height and pre-pregnancy weight reported on the birth certificate, diabetes (pregestational and/or gestational), hypertension (chronic/pregestational and/or gestational and/or eclampsia) and infant sex, as well as State and year of birth.

Birthweight *z*-score was calculated as ((actual weight − reference weight)/standard deviation for the reference population), as recommended by Land (2006), using sex-specific national standards (Talge *et al.*, 2014). Infants with *z*-scores of ≤ -1.28 were categorized as small-for-gestation (SGA) and infants with *z*-scores of ≥ 1.28 were categorized as large-for-gestation (LGA). ART factors and treatment parameters included infertility diagnoses (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal ligation, other tubal factors, uterine factor, unexplained, other (immunologic, chromosomal or other serious disease) and other-non-infertile (single woman or same sex partners)); sperm source (partner, donor, or mixed); use of assisted hatching and ICSI. Twin births were analyzed separately. Triplets and higher-order multiples were excluded, as well as all births of women with the infertility diagnosis of PGD. Singleton

data are shown in the Tables I, II, III and IV and twin data are presented in the Supplementary Tables SII, SIII and SIV.

Statistical analysis

Data from each State were processed to generate a common dataset. The only exclusions were a mother or father who was younger than 18 years of age or implausible values (gestational age <22 weeks or birthweight <300 g even if indicated as a live birth). Because most independent variables were categorized, missing values were included as a separate category. Based on expected birth defects rates per 10 000 live births averaged across the four study States, we expected our naturally conceived and ART study populations to provide 90% power to detect an effect size of 6–8% with a two-sided α of 0.05 for major defects and cardiovascular defects, and an effect size of 15–30% for blastogenesis defects, genitourinary defects, orofacial defects and gastrointestinal defects. We used logistic regression to model the risk of any birth defect, a major nonchromosomal birth defect (i.e. major defect not accompanied by a chromosomal defect), blastogenesis defects, cardiovascular defects, orofacial defects, gastrointestinal defects, genitourinary defects in male children, musculoskeletal defects, chromosomal defects and any defects by group (as defined previously), with naturally conceived children as the reference.

Within the ART group, risks were modeled by oocyte source-embryo state combinations, and among infants born from cycles using fresh embryos, additionally by the use of ICSI. All analyses were performed using SAS Version 9.4 software (SAS, Cary, NC, USA). We could not properly account for correlation within twin pairs because data on twinship were inconsistently available (data were not consistently provided for both twins in a pair in the natural and OI/IUI conceived births). The number of fetal heartbeats greater than plurality at birth was added to the models and changed the point estimates by at most 0.02; most were unchanged, so this factor was not retained in the models.

Given that the time period of this study was 2004–2016, there were women with more than one delivery resulting in a live birth. We were able to identify women who had more than one live birth among those who were ART-treated, but not among the natural and OI/IUI conceived women. Of the ART women who had a singleton live birth, 85.3% had only one singleton live birth; 13.4% had two singleton live births and 1.2% had 3–5 singleton live births. If all the children delivered by women with more than one live birth had the same birth defect, this would increase the estimate of the standard error by ~7%; however, only 12% of the children from a mother who had a child with one defect had more than one child with a birth defect. Therefore, the effect on the standard error and the resulting CI is ~1%. It is likely that the repeat live birth rate in fertile women is higher than that for ART women, but the rate of repeat defects is not likely to exceed that of the ART births. Even if the rate of repeat pregnancies was as high as 50%, the effect on the estimate of the standard error would be <5%.

Results

Characteristics of the study population

The final study population included 1 236 016 children (135 051 ART, 23 647 ART siblings, 9396 OI/IUI-conceived and 1 067 922 naturally conceived); 25 035 children (2.0%) had a major birth defect. There were 1 145 017 singleton children (78 362 ART, 22 301 ART siblings, 6597 OI/IUI-conceived and 1 037 757 naturally conceived), and 90 999 twin children (56 689 ART, 1346 ART siblings, 2799 OI/IUI-conceived and 30 165 naturally conceived); 21 998 singleton children (1.9%) and 3037 twin children (3.3%) had a major birth defect. The characteristics of the study population are shown in Table I for singletons and Supplementary Table SII for twins. The majority of women in the fertile group were between the ages of 18–29 years, compared to 30–37 years for the OI/IUI group and ART-treated women using autologous oocytes, and 41 years and older for ART-treated women using donor oocytes. Women with naturally conceived children were more likely to be Hispanic, and less likely to be white, to have completed college, be of lower parity, or have diabetes or hypertension compared to the other groups; the results were similar for twins. The prevalence of major birth defects (both chromosomal and nonchromosomal) among singletons was 1.9% among the naturally conceived group, 2.1% among the OI/IUI group, 2.0% among ART siblings, and within the ART group, 2.3–2.7% by oocyte source-embryo state category. Among twins, the prevalence of major birth defects was 3.2% among the naturally conceived group, 3.1% among the OI/IUI group, 3.9% among ART siblings and within the ART group, 3.0–3.8% by oocyte source-embryo state category. Within the ART group, women using autologous oocytes were more likely to have the diagnoses of male factor, endometriosis, ovulation disorders, other tubal factors or unexplained, whereas women using donor oocytes were more likely to have the diagnosis of diminished ovarian reserve or other reason for ART (includes immunologic, chromosomal or other serious disease), as shown in Table II. Sperm source and the use of ICSI was only reported for cycles using fresh embryos; in both autologous and donor oocyte cycles partner sperm were used in about 90% of cycles, and ICSI was used in more than 60% of cycles, higher in the presence of male factor infertility than without this diagnosis; the results were similar for twins (Tables I and II and Supplementary Tables SII and SIII).

Risk of birth defects in ART and non-ART groups

The results of the logistic regression models for singleton children are presented in Table III for singletons and Supplementary Table SIV for twins. Compared to naturally conceived children, ART singletons (conceived from autologous oocytes, fresh embryos without the use of ICSI) had increased risks of a major nonchromosomal birth defect (adjusted odds ratio (AOR) 1.18, 95% CI 1.05, 1.32), cardiovascular defects (AOR 1.20, 95% CI 1.03, 1.40) and any birth defect (AOR 1.18, 95% CI 1.09, 1.27). Compared to naturally conceived children, ART singletons (conceived from autologous oocytes, fresh embryos with the use of ICSI) the risks were increased for a major nonchromosomal birth defect (AOR 1.30, 95% CI 1.16,1.45 without male factor diagnosis; AOR 1.42, 95% CI 1.28, 1.57 with male factor diagnosis); blastogenesis defects (AOR 1.49, 95% CI 1.08, 2.05 without male factor; AOR 1.56, 95% CI 1.17, 2.08 with male factor); cardiovascular defects (AOR 1.28, 95% CI 1.10,1.48 without male factor; AOR 1.45, 95% CI 1.27, 1.66 with male factor); in addition, the risk for musculoskeletal defects was increased (AOR 1.34, 95% CI 1.01, 1.78 without male factor) and the risk for genitourinary defects in male infants was

Table I **Characteristics of the US study population (singleton births) by mode of conception.**

		Naturally	OI/IUI	ART	ART by oocyte source and embryo state*			
		Conceived	Conceived	Siblings	AF	AT	DF	DT
	All children, n	1 037 757	6597	22 301	50 418	18 029	6740	3175
	With major defects**, n (%)	19 493 (1.9)	141 (2.1)	449 (2.0)	1225 (2.4)	449 (2.5)	156 (2.3)	85 (2.7)
Maternal age	Mean ± SD	29.0 ± 5.8	33.7 ± 5.1	33.8 ± 4.7	35.0 ± 4.3	35.0 ± 4.2	42.2 ± 4.8	43.0 ± 5.2
(years)	(%) 18–29	53.0	20.6	16.9	10.2	9.4	1.3	1.5
	30–34	28.4	36.4	37.0	34.8	35.7	6.5	5.6
	35–37	11.0	20.2	24.2	24.9	26.5	8.0	8.0
	38–40	5.5	13.5	15.3	19.5	18.7	14.9	12.2
	41–43	1.8	6.6	5.4	9.5	8.0	24.9	21.3
	≥44	0.3	2.8	1.3	1.0	1.8	44.4	51.4
Ethnicity (%)	Hispanic	26.9	8.5	9.2	9.8	9.8	9.6	9.9
Race (%)	White	69.7	83.9	84.1	81.2	76.3	82.6	80.5
	Black	15.4	4.6	4.7	5.8	7.1	6.1	7.7
	American Indian/Alaskan Native	0.6	0.3	0.3	0.4	0.4	0.4	0.3
	Asian/Pacific Islander	7.7	9.1	8.2	10.4	13.4	8.4	9.4
	Other or missing	6.5	2.0	2.7	2.2	2.7	2.4	2.2
Maternal	<High school	15.3	1.8	1.4	1.3	2.1	1.4	1.5
Education (%)	High school graduate/GED	24.2	8.3	7.7	7.7	6.7	6.6	6.1
	Some college/associate degree	26.8	21.1	17.4	19.9	21.7	19.1	22.3
	Bachelor's degree	19.8	34.7	39.0	37.8	39.1	37.7	37.1
	Post graduate degree	12.5	33.9	32.7	32.1	29.5	33.9	31.9
	Missing	1.4	0.2	1.7	1.3	0.9	1.4	1.1
Parity (%)	0	40.1	62.5	37.6	68.0	50.2	67.6	48.3
	1	32.1	27.0	35.7	23.3	33.1	21.4	32.6
	2+	27.8	10.5	26.7	8.7	16.8	11.0	19.2
BMI (kg/m^2)	Mean ±SD	26.1 ± 6.2	26.2 ± 6.3	25.2 ± 5.3	25.2 ± 5.5	25.1 ± 5.4	25.2 ± 5.3	25.5 ± 5.6
	(%) 12–24	52.5	52.9	58.9	59.8	60.6	59.0	57.2
	25–29	25.4	23.6	24.5	23.2	23.2	24.7	24.9
	30–59	22.0	23.5	16.6	16.9	16.2	16.3	17.9
	Missing	50.5	48.4	62.3	55.0	33.7	53.4	39.9
Diabetes (%)	Pre-gestational or gestational	5.2	9.4	5.0	7.0	7.6	8.5	9.7
Hypertension (%)	Pre-gestational or gestational	5.3	8.7	4.7	6.5	8.3	13.2	13.2
Cesarean (%)	Cesarean	30.4	37.7	45.2	42.6	50.2	63.7	66.1
Length of	Mean weeks ± SD	38.7 ± 1.9	38.5 ± 2.4	38.5 ± 2.0	38.4 ± 2.2	38.5 ± 2.2	38.2 ± 2.3	37.9 ± 2.5
gestation	(%) <28 weeks	0.5	1.0	0.7	0.8	0.8	0.6	1.2
	28–32 weeks	1.1	2.0	0.9	1.7	1.4	2.2	2.8
	33–36 weeks	6.1	7.7	6.4	8.6	8.4	11.8	13.1
	≥37 weeks	92.4	89.2	92.0	88.9	89.4	85.4	82.9
Birthweight	Mean grams ± SD	3312 ± 553	3280 ± 634	3358 ± 566	3238 ± 605	3374 ± 612	3241 ± 637	3214 ± 664
	300–999 grams	0.5	1.1	0.7	0.9	0.8	0.7	1.1
	1000–1499 grams	0.5	1.0	0.4	0.9	0.7	1.4	1.3
	1500–2499 grams	5.0	6.6	4.1	7.2	5.2	8.6	9.5
	≥2500 grams	94.0	91.3	94.8	91.1	93.3	89.4	88.1
Birthweight	Mean ± SD	−0.01 ± 0.97	0.01 ± 0.98	0.14 ± 0.97	−0.06 ± 0.97	0.22 ± 0.99	0.05 ± 1.00	0.11 ± 1.00
Z-score***	SGA, *Z*-score ≤−1.28	8.3	8.7	5.9	9.5	5.2	8.1	6.9
	LGA, *Z*-score ≥1.28	9.0	9.7	11.5	8.3	13.5	10.3	11.1
Infant Sex (%)	Male	51.2	52.2	51.9	51.3	52.1	51.3	51.1

*Oocyte source-embryo state combinations include AF, AT, DF and DT.

**Includes both chromosomal and nonchromosomal defects.

***Infants with *z*-scores of ≤−1.28 were categorized as SGA and infants with *z*-scores of ≥1.28 were categorized as LGA.

AF, autologous-fresh; AT, autologous-thawed; DF, donor-fresh; DT, donor-thawed; GED, general educational development; LGA, large-for-gestation; OI, ovulation induction; SGA, small-for-gestation.

Table II Characteristics (%) of the ART group (singleton births) by oocyte source and embryo state.

Oocyte source-embryo state*		AF	AT	DF	DT
n, Children		50 418	18 029	6740	3175
Diagnoses	Male factor	38.1	35.9	17.4	15.7
	Endometriosis	11.0	10.2	6.0	5.8
	Ovulation disorders	16.2	20.4	3.7	4.6
	Diminished ovarian reserve	15.7	11.9	77.7	75.0
	Tubal ligation	1.7	1.4	0.8	0.9
	Tubal-hydrosalpinx	1.4	1.6	0.7	0.5
	Tubal-other	13.5	13.8	5.5	6.4
	Uterine factor	4.3	5.6	5.8	6.9
	Unexplained	17.0	17.1	4.3	4.3
	Other-RFA**	9.0	9.5	16.1	17.7
	Noninfertile	0.4	0.6	0.5	1.0
# Diagnoses	One	75.3	75.5	67.9	68.6
	Two or more	24.4	24.3	32.0	31.1
	Missing	0.3	0.3	0.1	0.2
Sperm source	Partner	95.1	–	90.1	–
	Mixed	0.2	–	0.8	–
	Donor	4.5	–	9.1	–
	Missing	0.2	–	0.0	–
Assisted hatching	None	64.3	53.3	76.3	51.8
	Some	3.1	2.3	2.5	1.7
	All	32.4	44.4	21.2	46.4
	Missing	0.2	0.0	0.0	0.1
ICSI (all births)	None	32.6	–	28.4	–
	Some	6.1	–	6.4	–
	All	60.9	–	65.2	–
	Missing	0.4	–	0.0	–
ICSI with male factor diagnosis	None	8.8	–	8.6	–
	Some	4.3	–	5.2	–
	All	86.6	–	86.2	–
	Missing	0.2	–	0.0	–
ICSI without male factor diagnosis	None	47.2	–	32.6	–
	Some	7.3	–	6.6	–
	All	45.1	–	60.8	–
	Missing	0.4	–	0.0	–
Number of fetal heartbeats***	One	92.1	94.7	89.7	94.2
	Two	7.0	4.8	9.1	5.2
	>Two	0.8	0.4	1.1	0.5

*Oocyte source-embryo state combinations include AF, AT, DF and DT.
**Other RFA includes immunologic, chromosomal or other serious disease.
***Fetal heartbeats on ultrasound at 6 weeks' gestation.
RFA, reason for ART.

increased (AOR 1.33, 95% CI 1.08, 1.65 with male factor). Compared to naturally conceived children, ART singleton siblings had increased risks of musculoskeletal defects (AOR 1.32, 95% CI 1.04, 1.67) and any defect (AOR 1.15, 95% CI 1.08, 1.23). ART twins (conceived with autologous oocytes, fresh embryos, without ICSI) were at increased risk of chromosomal defects (AOR 1.89, 95% CI 1.10, 3.24) and ART twin siblings were at increased risk of any defect (AOR 1.26, 95% CI 1.01, 1.57). Assisted hatching was not associated with birth defects in singletons or twins (data not shown). This analysis also confirmed known associations between risks for birth defects and older maternal age, higher BMI, diabetes, hypertension, and male sex of the infant, independent of subfertility and ART conception.

Risk of birth defects by ART treatment parameters

Table IV shows the rates per 10 000 singleton children and risks for each birth defect category for ART births by oocyte source-embryo state combinations, and the use of ICSI in fresh embryos. Among children conceived with fresh embryos, compared to children conceived from autologous oocytes without ICSI, the risks were increased for a major nonchromosomal defect (AOR 1.18, 95% CI 1.03, 1.35), blastogenesis defect (AOR 1.65, 95% CI 1.08, 2.51), gastrointestinal defect (AOR 2.21, 95% CI 1.28, 3.82), and any defect (AOR 1.11, 95% CI 1.01, 1.22) with autologous oocytes and ICSI, and the risk of chromosomal defects was decreased (AOR 0.18, 95% CI 0.05, 0.67) with donor oocytes and ICSI. In models including children conceived with fresh and thawed embryos, compared to children conceived with autologous oocytes and fresh embryos, the use of donor oocytes was associated with decreased risks of chromosomal defects (donor, fresh, AOR 0.12, 95% CI 0.04, 0.43; donor, thawed, AOR 0.09, 95% CI 0.01, 0.67).

Discussion

We found that singleton infants conceived with ART (using autologous oocytes, fresh embryos, and without ICSI) were 18% more likely than naturally conceived infants to have a major nonchromosomal birth defect; with ICSI in the absence of male factor diagnosis, the risk increased to 30%; with male factor, the risk increased to 42%. The 18% increased risk of a major nonchromosomal birth defect in singleton infants conceived with ART without ICSI (~36% of ART births), the 30% increased risk with ICSI without male factor (~33% of ART births), and the 42% increased risk with ICSI and male factor (~31% of ART births) translates into an estimated excess of 386 major birth defects among the 68 908 singleton children born by ART in 2017.

Our prevalence rates of birth defects are in accord with both US and European rates (State Birth Defects Surveillance Program Directory, 2016; EUROCAT prevalence rates, 2020), as well as our prior research in Massachusetts (Luke *et al.*, 2017a,b). These findings are consistent with the pooled estimate of 1.32 (95% CI 1.24, 1.42) in 45 studies of ART reported by Hansen *et al.* (2013). Our findings of higher birth defects rates among twins compared to singletons are also in accord with prior studies (Hansen *et al.*, 2013).

Comparison to other published studies is challenging due to differences in case ascertainment, birth defects definitions, reporting of ART treatment parameters, time periods and periods of follow-up, and failure to differentiate births by plurality. In the CDC population-based 2000–2010 study in Florida, Massachusetts and Michigan, Boulet *et al.* (2016) reported on a limited number of birth defects because of differences in case ascertainment across States (passive surveillance in

Table III Risk of birth defects among singletons by maternal characteristics and mode of conception.*

		Major birth defect**		Blastogenesis		Cardiovascular		Musculoskeletal		Genitourinary-male		Chromosomal		Any birth defect	
		AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI	AOR	95% CI
Group***	Naturally conceived	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	OI/IUI conceived	1.16	0.97, 1.38	1.11	0.66, 1.85	0.96	0.74, 1.24	1.29	0.86, 1.94	1.25	0.90, 1.73	1.00	0.60, 1.68	1.12	0.99, 1.26
	ART siblings	1.08	0.98, 1.19	1.19	0.90, 1.58	1.10	0.96, 1.26	**1.32**	**1.04, 1.67**	0.96	0.78, 1.19	0.94	0.69, 1.27	**1.15**	**1.08, 1.23**
	ART-auto-fresh, no ICSI	**1.18**	**1.05, 1.32**	0.99	0.69, 1.42	**1.20**	**1.03, 1.40**	1.19	0.89, 1.57	1.11	0.88, 1.41	0.65	0.44, 0.95	**1.18**	**1.09, 1.27**
	ART-auto-fresh, yes ICSI-no MF	**1.30**	**1.16, 1.45**	**1.49**	**1.08, 2.05**	**1.28**	**1.10, 1.48**	**1.34**	**1.01, 1.78**	1.09	0.85, 1.39	0.89	0.63, 1.26	**1.22**	**1.13, 1.32**
	ART-auto-fresh, yes ICSI-yes MF	**1.42**	**1.28, 1.57**	**1.56**	**1.17, 2.08**	**1.45**	**1.27, 1.66**	1.25	0.96, 1.64	**1.33**	**1.08, 1.65**	0.93	0.66, 1.33	**1.38**	**1.29, 1.48**
Maternal	18–29	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
Age (years)	30–34	**1.09**	**1.05, 1.12**	0.92	0.83, 1.02	**1.17**	**1.11, 1.23**	0.97	0.89, 1.06	1.08	1.00, 1.17	**1.76**	**1.52, 2.03**	**1.07**	**1.05, 1.10**
	35–37	**1.11**	**1.06, 1.16**	0.83	0.72, 0.96	**1.34**	**1.26, 1.43**	0.91	0.81, 1.04	1.11	1.00, 1.23	**3.46**	**2.95, 4.05**	**1.13**	**1.10, 1.17**
	38–40	**1.10**	**1.03, 1.17**	0.96	0.80, 1.14	**1.52**	**1.40, 1.64**	0.97	0.83, 1.14	1.03	0.90, 1.18	**6.79**	**5.800, 7.96**	**1.23**	**1.18, 1.28**
	41–43	**1.13**	**1.03, 1.24**	1.10	0.85, 1.43	**1.77**	**1.59, 1.97**	1.12	0.89, 1.42	1.19	0.98, 1.45	**15.4**	**12.99, 18.25**	**1.42**	**1.34, 1.51**
	≥44	**1.30**	**1.07, 1.59**	**1.80**	**1.12, 2.88**	**2.58**	**2.11, 3.16**	1.42	0.89, 2.26	1.32	0.87, 2.00	**28.7**	**22.47, 36.67**	**1.68**	**1.49, 1.90**
BMI (kg/m^2)	12–24	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	25–29	1.01	0.97, 1.06	1.00	0.88, 1.14	1.03	0.96, 1.09	1.04	0.93, 1.17	0.99	0.89, 1.09	1.10	0.94, 1.30	1.00	0.97, 1.04
	30–59	**1.18**	**1.12, 1.24**	1.10	0.96, 1.26	**1.23**	**1.16, 1.31**	**1.25**	**1.11, 1.41**	0.96	0.86, 1.08	1.09	0.92, 1.29	**1.13**	**1.10, 1.17**
Diabetes	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Pre- or gestational	**1.34**	**1.27, 1.41**	**1.46**	**1.25, 1.69**	**1.47**	**1.37, 1.57**	1.05	0.90, 1.22	**1.14**	**1.01, 1.30**	1.11	0.93, 1.32	**1.26**	**1.21, 1.30**
Hypertension	None	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
	Pre- or gestational	**1.43**	**1.36, 1.51**	1.13	0.96, 1.33	**1.49**	**1.40, 1.60**	1.04	0.90, 1.21	**1.71**	**1.54, 1.91**	1.00	0.83, 1.21	**1.34**	**1.29, 1.39**
Infant sex	Female	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	–	–	1.00	Reference	1.00	Reference
	Male	**1.53**	**1.49, 1.58**	**1.17**	**1.08, 1.27**	0.96	0.92, 1.00	**1.44**	**1.34, 1.54**	–	–	1.01	0.92, 1.11	**1.55**	**1.52, 1.58**

*Models adjusted for all factors listed above, as well as maternal race and ethnicity, education, parity, and State and year of birth. ART births limited to autologous-fresh with partner ejaculated sperm. Bolded values are significantly increased.
**Major defects are limited to nonchromosomal only.
***Group (n, children): naturally conceived (1 066 652); OI/IUI conceived (6899); non-ART siblings (22 821); ART-auto-fresh, no ICSI (all infertility diagnoses, no ICSI: 16 433); ART-auto-fresh, yes ICSI-no MF (yes ICSI, no male factor diagnosis: 14 071); ART-auto-fresh, yes ICSI-yes MF (yes ICSI, yes male factor diagnosis: 16 629). AOR, adjusted odds ratio.
Major birth defects as defined by the National Birth Defects Prevention Network (NBDPN) (see Supplementary Table SI).
Any birth defect is any ICD-9 code with the first 3 digits 740–759, and any ICD-10 code inclusive of Q00.0–07.9, 10–18.9, 20–28.9, 30–45.9, 50–56.4, 60–87.89 and 89–99.9.

Table IV **Risk of type of birth defect among IVF singletons by oocyte source-embryo state and use of ICSI.***

	Fresh embryos only					All embryos				
Birth defect	**Oocyte source**	**Use of ICSI**	**Rate per 10 000**	**AOR**	**95% CI**	**Oocyte source**	**Embryo state**	**Rate per 10 000**	**AOR**	**95% CI**
Nonchromosomal	Autologous	No	189.3	1.00	Reference	Autologous	Fresh	223.2	1.00	Reference
	Autologous	Yes	238.8	**1.18**	**1.03, 1.35**	Autologous	Thawed	234.4	1.00	0.89, 1.13
	Donor	No	218.6	1.08	0.75, 1.54	Donor	Fresh	226.6	0.94	0.76, 1.15
	Donor	Yes	234.0	1.14	0.87, 1.49	Donor	Thawed	264.4	1.08	0.83, 1.40
Blastogenesis	Autologous	No	18.8	1.00	Reference	Autologous	Fresh	25.9	1.00	Reference
	Autologous	Yes	29.2	**1.65**	**1.08, 2.51**	Autologous	Thawed	25.4	0.99	0.69, 1.41
	Donor	No	20.8	1.23	0.40, 3.79	Donor	Fresh	23.7	0.78	0.42, 1.45
	Donor	Yes	20.4	1.24	0.52, 2.96	Donor	Thawed	50.4	1.68	0.88, 3.19
Cardiovascular	Autologous	No	105.0	1.00	Reference	Autologous	Fresh	124.7	1.00	Reference
	Autologous	Yes	135.2	1.14	0.95, 1.37	Autologous	Thawed	132.1	1.02	0.87, 1.19
	Donor	No	114.5	0.92	0.57, 1.49	Donor	Fresh	125.9	0.90	0.68, 1.18
	Donor	Yes	136.3	1.03	0.72, 1.47	Donor	Thawed	122.8	0.87	0.60, 1.25
Orofacial	Autologous	No	16.4	1.00	Reference	Autologous	Fresh	19.8	1.00	Reference
	Autologous	Yes	20.8	1.20	0.76, 1.91	Autologous	Thawed	16.6	0.81	0.53, 1.24
	Donor	No	15.6	0.86	0.23, 3.21	Donor	Fresh	13.3	0.68	0.30, 1.53
	Donor	Yes	13.6	0.80	0.28, 2.26	Donor	Thawed	22.0	1.09	0.44, 2.71
Gastrointestinal	Autologous	No	10.3	1.00	Reference	Autologous	Fresh	17.6	1.00	Reference
	Autologous	Yes	21.8	**2.21**	**1.28, 3.82**	Autologous	Thawed	15.5	0.88	0.57, 1.38
	Donor	No	10.4	1.07	0.22, 5.14	Donor	Fresh	11.8	0.56	0.24, 1.30
	Donor	Yes	9.1	0.92	0.27, 3.20	Donor	Thawed	25.2	1.19	0.49, 2.87
Genitourinary	Autologous	No	85.3	1.00	Reference	Autologous	Fresh	100.2	1.00	Reference
(male infants)	Autologous	Yes	105.3	1.12	0.84, 1.49	Autologous	Thawed	118.7	1.14	0.90, 1.44
	Donor	No	76.5	0.72	0.33, 1.60	Donor	Fresh	103.9	0.86	0.56, 1.32
	Donor	Yes	127.4	1.14	0.67, 1.96	Donor	Thawed	129.4	1.04	0.62, 1.76
Musculoskeletal	Autologous	No	31.0	1.00	Reference	Autologous	Fresh	35.0	1.00	Reference
	Autologous	Yes	35.1	1.17	0.83, 1.65	Autologous	Thawed	26.0	0.72	0.51, 1.01
	Donor	No	41.6	1.14	0.49, 2.63	Donor	Fresh	35.5	0.78	0.46, 1.34
	Donor	Yes	31.8	0.90	0.44, 1.83	Donor	Thawed	31.5	0.67	0.32, 1.39
Chromosomal	Autologous	No	16.4	1.00	Reference	Autologous	Fresh	20.4	1.00	Reference
	Autologous	Yes	21.8	1.43	0.90, 2.27	Autologous	Thawed	13.8	0.66	0.42, 1.05
	Donor	No	0.0	–	–	Donor	Fresh	4.4	**0.12**	**0.04, 0.43**
	Donor	Yes	6.8	**0.18**	**0.05, 0.67**	Donor	Thawed	3.1	**0.09**	**0.01, 0.67**
Any birth defect	Autologous	No	412.7	1.00	Reference	Autologous	Fresh	484.8	1.00	Reference
(740.0–759.9)	Autologous	Yes	520.6	**1.11**	**1.01, 1.22**	Autologous	Thawed	492.0	0.95	0.88, 1.04
	Donor	No	426.9	0.89	0.69, 1.15	Donor	Fresh	488.7	0.91	0.79, 1.05
	Donor	Yes	517.9	1.04	0.87, 1.25	Donor	Thawed	503.6	0.93	0.77, 1.12

*Models adjusted for maternal age, BMI, education, race and ethnicity, parity, diabetes and hypertension (pre-gestational and gestational), state and year of birth, and infant sex. Bolded values are significant. Major birth defects as defined by the NBDPN (see Supplementary Table SI). Any birth defect is any ICD-9 code with the first 3 digits 740–759, and any ICD-10 code inclusive of Q00.0–07.9, 10–18.9, 20–28.9, 30–45.9, 50–56.4, 60–87.89 and 89–99.9.

Florida and Michigan, and active surveillance in Massachusetts), focusing only on defects usually diagnosed at birth. Although their reported singleton major nonchromosomal birth defects rates (per 10 000 live births) by oocyte source-embryo state combinations were much lower (ranging from 56 to 79) compared to our study (189 to 264), both studies found no significant difference by the combination of these two factors. Our study also differed because our ART-conceived group, which was compared to natural and OI/IUI conceived groups, included only infants conceived using autologous oocytes and fresh embryos (to be more physiologically comparable to naturally conceived infants), whereas in the CDC study the ART group included both autologous and donor oocytes as well as fresh and thawed embryos.

Also, in contrast, our analyses did not show an increased risk of birth defects with the use of assisted hatching (data not shown), whereas the CDC study showed a 55% increased risk; other studies have also reported no increased risk (Jwa *et al.*, 2015).

Blastogenesis risk

Halliday *et al.* (2010), in their singleton study of 20 838 non-ART controls and 6946 ART children, reported increased blastogenesis defects risks with both ICSI (AOR 2.33, 95% CI 1.12, 4.87) and fresh embryos (AOR 3.65, 95% CI 2.02, 6.59). Our results indicate lower blastogenesis risks compared to those reported by Halliday, including increased risks with ICSI in the absence and presence of male factor (AOR 1.49, 95% CI 1.08, 2.05, and AOR 1.56, 95% CI 1.17, 2.08, respectively among singletons, and AOR 1.50, 95% CI 1.01, 2.23 with ICSI in the absence of male factor among twins). Other factors we found to be significantly associated with an increased risk of blastogenesis defects in singletons were older maternal age (≥44 years, AOR 1.80, 95% CI 1.12, 2.88), diabetes (pre-pregnancy or gestational, AOR 1.46, 95% CI 1.25, 1.69), and male infant sex (AOR 1.17, 95% CI 1.08, 1.27 in singletons and AOR 1.30, 95% CI 1.01, 1.67 in twins). These differences may have been due to our exclusion of cardiac defects in defining blastogenesis defects, and limiting to live births only, as well as changes in culture media over the study periods (1991–2004 in the Halliday study, and 2004–2016 in our study); the Halliday study also included pregnancies terminated for a birth defect at any gestation. As blastogenesis defects may have an environmental etiology, including aspects of ART treatment, these associations should be investigated further.

ICSI and birth defects risk

As a commonly used procedure in ART, the use of ICSI has increased in the USA from 11% in 1995 to 67% in 2017 (Toner *et al.*, 2016; Centers for Disease Control and Prevention, 2019). This trend is also evident internationally, with 66% of cycles using ICSI in 2010, ranging from 56% of cycles in Asia to 96% of cycles in the Middle East (Dyer *et al.*, 2016). The use of ICSI offers hope of genetic parenthood for men with profound oligospermia (low sperm count) and, by means of testicular biopsy and epididymal aspiration, even for men with azoospermia (absence of sperm). However, it is increasingly being used even in the absence of male factor infertility. There are several theoretical concerns, though, regarding ICSI and the potential risks for the offspring (de Kretser, 1995; Palermo, 2008; Woldringh *et al.*, 2010): the risks of using sperm that potentially carry genetic abnormalities; the risks of using sperm with structural defects; the potential for mechanical and biochemical damage by introducing foreign material into the oocyte; and the risks associated with circumventing natural selection by injecting a single spermatozoon. The analyses of the outcomes of children born after ICSI have shown mixed results, including a 3-fold-increased risk of congenital heart defects (Tararbit *et al.*, 2013), a twofold risk of major birth defects and a 50% increased risk of minor birth defects (Hansen *et al.*, 2002; Katalinic *et al.*, 2004; Yan *et al.*, 2011; Davies *et al.*, 2012a; Farhi *et al.*, 2013), while other studies have shown no difference (Lie *et al.*, 2005). Our results, which were limited to children conceived using fresh embryos, indicated a 30% increased risk of a major nonchromosomal birth defect with the use of ICSI in the absence of male factor diagnosis, increasing to 42% in the presence of male factor diagnosis, compared to naturally conceived singletons. These findings support the judicious use of ICSI only when medically necessary in ART-treated patients.

Fresh versus thawed embryos and birth defect risk

The use of frozen embryo transfer has increased by more than 80% since 2006 owing to better cryo-preservation techniques, improved live birth rates, lower risk of ectopic pregnancies, and more physiologically normal hormonal and endometrial environments (Toner *et al.*, 2016; Centers for Disease Control and Prevention, 2019). Results indicate that singletons born after frozen embryo transfer have comparable or lower risks for low birthweight, SGA birthweight and preterm birth compared to singletons born after fresh ART, but worse outcomes compared to singletons born after natural conception, including an excess of LGA birthweights, pregnancy-induced hypertension and placenta accreta (Wada *et al.*, 1994; Källén *et al.*, 2005; Belva *et al.*, 2008, 2016; Shih *et al.*, 2008; Pinborg *et al.*, 2010; Luke *et al.*, 2019, 2020; Hwang *et al.*, 2019). Belva *et al.* (2008) reported rates of major malformations to be highest in children born from cryopreserved embryos with ICSI (6.4%) compared to children born from cryopreserved embryos without ICSI (3.1%) and fresh embryos with ICSI (3.4%). Other studies have reported malformation rates in frozen cycles ranging from 1.0% (Wada *et al.*, 1994) to 8.7% (Källén *et al.*, 2005). Pinborg *et al.* (2010), in their study of Danish singleton births in 1995–2002, reported higher nonsignificant differences in major birth defects rates among infants conceived using fresh embryos (5.9%, 5.8% with ICSI) and thawed embryos (5.4%; 4.5% with ICSI) compared to infants of fertile controls (4.7%). Recent analyses of infants born in 2004–2013 in Massachusetts confirm small but nonsignificant differences in birth defect risks from fresh versus thawed embryos (1.8% vs 1.7%, respectively for nonchromosomal defects) (Hwang *et al.*, 2019). A Belgian study of births in 2008–2013 reported similar results for singletons (fresh, 2.8%, thawed, 2.6%) and twins (fresh, 2.7%, thawed, 2.4%) (Belva *et al.*, 2016). Our findings are in line with these prior reports, with frequencies of major birth defects among singletons of 2.4% and 2.5% for autologous-fresh and autologous-thawed, and 2.3% and 2.7% for donor-fresh and donor-thawed, respectively; and among twins of 3.4% and 3.8% for autologous-fresh and autologous-thawed, and 3.0% and 3.5% for donor-fresh and donor-thawed, respectively. Among singleton ART births comparing to births from autologous oocytes and fresh embryos, there were no significant differences in the risks of birth defects, except for chromosomal defects, which were decreased with the use of donor oocytes (fresh, AOR 0.12, 95% CI 0.04, 0.43; thawed, AOR 0.09, 95% CI 0.01, 0.67).

Sibling studies

The choice of an appropriate comparison group in infertility research poses a special challenge. Although most studies compare women treated for infertility to fertile women, this approach has several potential disadvantages, including differences in age, socioeconomic status, education and reproductive history. Comparisons within families, as repeat pregnancies to the same woman, have the advantage of eliminating the fixed effects of the parents (mainly the genetic contribution), with adjustments possible for her change in age, parity, and, if appropriate, method of conception. In our prior studies of siblings in

Massachusetts, declining fertility status, with or without ART, was associated with increasing risks for adverse outcomes, greatest for women whose fertility status declined the most between the two pregnancies (Luke *et al.*, 2016a). In addition, we previously demonstrated that among singleton siblings both conceived with ART, frozen embryo state was associated with an increased risk of LGA birthweight (AOR 1.74, 95% CI 1.45, 2.08), with a birthweight difference of 222 g (SE 11) (Luke *et al.*, 2017c). Henningsen *et al.* (2011) reported similar results in singleton siblings with fresh versus frozen embryo status, with a birthweight difference of 286 g. Shih *et al.* (2008) in their large Australian study reported a difference of 244 g in ART-conceived siblings conceived using fresh versus frozen embryos. Only one study reported on the risk of birth defects in siblings. In an additional sibling analysis to their Australian study (Davies *et al.*, 2012a), Davies *et al.* (2012b) reported an increased risk of birth defects among ART-conceived siblings compared to naturally conceived siblings (crude odds ratio, 1.50, 95% CI, 1.08, 2.09). Among singleton ART siblings, our analysis showed increased risks of any defect (AOR 1.15, 95% CI 1.08, 1.23) and musculoskeletal defects (AOR 1.32, 95% CI 1.04, 1.67), and among twin ART siblings, increased risks of any defect (AOR 1.26, 95% CI 1.01, 1.57).

Our findings of an increased risk of birth defects among ART siblings who were conceived without ART suggests that subfertility may be a contributing factor. It remains difficult to separate the relative contribution of the biology of the subfertile couple versus aspects of the ART treatment to this increased risk. This information regarding birth defects should be included when counseling patients about the risks and benefits of ART. In addition, the larger context of risk versus benefit of ART versus other treatment options, such as expectant management and controlled ovarian stimulation with IUI, should be considered. ART treatment will typically lead to a shorter time to conception, mitigating the effect of advancing maternal age. ART also enables a more controllable situation with respect to the risk of multiple gestation compared with ovarian stimulation with IUI, with twins and triplets associated with many serious adverse consequences for both the mother and the children. Furthermore, some couples have fertility factors that are not treatable other than by ART. The potential for increased risk of birth defects associated with ART needs to be balanced against the potential risks associated with other options.

Challenge of monitoring of births and birth defects from ART in the USA

Unlike other countries that track their citizen's health from cradle to grave, the USA does not have a uniform system to monitor health. The US Certificate of Live Birth is the only consistent mechanism to assess population-based data on births for all States and territories. Revised periodically, the 2003 version of the birth certificate includes checkbox questions regarding the use of infertility treatment. Although the birth certificate has been suggested as a mechanism to identify children conceived with infertility treatment (Lynch *et al.*, 2011), several validation studies of the accuracy of ART indicated on the birth certificate have reported low sensitivity (ranging from 27 to 28% overall, higher with multiples, 43%), with only 36–50% accurately reported (Zhang *et al.*, 2010; Cohen *et al.*, 2014; Thoma *et al.*, 2014; Luke *et al.*, 2016b). Birth defects have also been indicated on the birth certificate, but validation studies of the 1989 and 2003 versions compared to birth defects registry data have shown low sensitivities (23% and 19.1%, respectively) (Boulet *et al.*, 2011; Salemi *et al.*, 2017). Birth defects have also been included in the outcome data of ART cycles in the SART CORS, but again, validation studies showed low sensitivity (38.6% for any birth defect, ranging from 18.4 to 50% for specific birth defect categories) (Stern *et al.*, 2016), making research findings based on these data questionable (Xiong *et al.*, 2017; Kirby and Boulet, 2017). The birth defect variables have since been removed from research data provided by SART. When the birth certificate is used as the sole data source of both infertility treatment and birth defects, the research is doubly flawed (Shechter-Maor *et al.*, 2018).

Strengths

This study has a number of strengths, including a large sample size, population-based design, and contemporary time period. The four study States include racially and ethnically diverse populations, with high linkage rates to the SART CORS, vital records, and birth defects registries, and their birth defects registries utilize the similar case definitions and data collected. We were able to stratify our analysis by plurality, non-ART and ART conception, and additionally within the ART group by oocyte source, embryo state, and the use of ICSI, as well as including naturally conceived ART siblings. The infertility data and birth defects data were independently collected, minimizing the risk of ascertainment bias.

Limitations

This study is subject to several limitations. In the SART CORS database, it was not possible to differentiate method of embryo freezing (slow-freezing vs vitrification); data on ICSI was only available in the fresh embryo ART group, not the thawed embryo group; and data were unavailable on duration of infertility, which has been reported to be related to birth defect risk (Ghazi *et al.*, 1991; Zhu *et al.*, 2006). Data on preimplantation testing were not available, other than the infertility diagnosis of PGD; these births were excluded from the analysis. For the OI/IUI group, it was not possible to differentiate type of non-ART treatment utilized (e.g. IUI, ovulation stimulation). We were not able to reconstruct sibling sets in twin births. Data on birth defects were not available on miscarriages, terminations or stillbirths, only on live births; this limitation is also noted in other population-based studies (Källén *et al.*, 2005, 2010), which for legal reasons could not be included in the linkages or analyses, making it impossible to study conditions that are more likely to be terminated after prenatal detection. In addition, data were unavailable on imprinting disorders. Because of the lack of a national registry for non-ART infertility procedures, the OI/IUI group is likely underrepresented, with some treated women included in the naturally conceived groups. This underrepresentation would tend to bias toward finding less of a difference between the OI/IUI and naturally conceived groups. Although we limited the ART siblings to those naturally conceived, as indicated in the Materials and Methods, there is a possibility that this group also included children conceived with OI or IUI, or were conceived with ART treatment performed outside the USA or ART treatments not nationally reported.

Conclusion

The use of ART is associated with increased risks of a major nonchromosomal birth defect, cardiovascular defect, and any defect in singleton children, and chromosomal defects in twins; the use of ICSI increases this risk further, highest with a male factor diagnosis. The relative contribution of ART treatment parameters versus the biology of the couple to this increased risk remains unclear.

Supplementary data

Supplementary data are available at *Human Reproduction* on-line.

Data availability

The data used in this analysis were obtained from private (SART CORS) and public (vital records, birth defects registries) sources, under data use agreements and confidentiality pledges assuring that the data would not be shared or distributed, and therefore are not available to other investigators.

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Authors' roles

B.L. designed the study. E.W. provided the ART data, and N.E.F., M.L.B., S.C.F., M.M.Y., M.K.E., M.A.C. provided the birth certificate and birth defect data. M.B.B. merged the data and fitted the models. All authors interpreted the data. B.L. drafted the manuscript, and it was finalized by all co-authors. The final version of the manuscript was approved by all authors. The authors agreed upon the listing of authors.

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Conflict of interest

E.W. is a contract vendor to the Society for Assisted Reproduction; all other authors have no conflict of interest related to this work.

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