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Assisted Reproductive Technology and Birth Defects Among Liveborn Infants in Florida, Massachusetts, and Michigan, 2000–2010

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Abstract

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IMPORTANCE—Use of assisted reproductive technology (ART) has been associated with increased risks for birth defects. Variations in birth defect risks according to type of ART procedure have been noted, but findings are inconsistent.

OBJECTIVES—To examine the prevalence of birth defects among liveborn infants conceived with and without ART and to evaluate risks associated with certain ART procedures among ART-conceived infants.

DESIGN, SETTING, AND PARTICIPANTS—Used linked ART surveillance, birth certificates, and birth defects registry data for 3 states (Florida, Massachusetts, and Michigan). Methods for ascertaining birth defect cases varied by state. Resident live births during 2000 to 2010 were included, and the analysis was conducted between Feburary 2015 and August 2015.

EXPOSURES—Use of ART among all live births and use of certain ART procedures among ART births.

MAIN OUTCOME AND MEASURES—Prevalence of selected chromosomal and nonchromosomal birth defects that are usually diagnosed at or immediately after birth.

RESULTS—Of the 4 618 076 liveborn infants between 2000 and 2010, 64 861 (1.4%) were conceived using ART. Overall, the prevalence of 1 or more of the selected nonchromosomal defects was 58.59 per 10 000 for ART infants (n = 389) vs 47.50 per 10 000 for non-ART infants (n = 22 036). The association remained significant after adjusting for maternal characteristics and year of birth (adjusted risk ratio [aRR], 1.28; 95%CI, 1.15–1.42). Similar differences were observed for singleton ART births vs their non-ART counterparts (63.69 per 10 000 [n = 218] vs 47.17 per 10 000 [n = 21 251]; aRR, 1.38; 95%CI, 1.21–1.59). Among multiple births, the prevalence of rectal and large intestinal atresia/stenosis was higher for ART births compared with non-ART births (aRR, 2.39; 95%CI, 1.38–4.12). Among ART births conceived after fresh embryo transfer, infants born to mothers with ovulation disorders had a higher prevalence of nonchromosomal birth defects (aRR, 1.53; 95%CI, 1.13–2.06) than those born to mothers without the diagnosis, and use of assisted hatching was associated with birth defects among singleton births (aRR, 1.55; 95%CI, 1.10–2.19). Multiplicity-adjusted *P* values for these associations were greater than .05.

CONCLUSIONS AND RELEVANCE—Infants conceived after ART had a higher prevalence of certain birth defects. Assisted hatching and diagnosis of ovulation disorder were marginally associated with increased risks for nonchromosomal birth defects; however, these associations may be caused by other underlying factors.

In 2012, approximately 1.5%of liveborn infants in the United States were conceived using assisted reproductive technology (ART), defined as fertility treatments in which eggs or embryos are handled outside the body.[1] Since the birth of the first ART-conceived infant in the United States in 1981, ART use has increased rapidly; more than 157000 cycles were performed in 2012.[2] Although ART is generally considered safe, findings from registry-based cohort studies[3–5] andmeta-analyses,[6–8] primarily conducted in non-US populations, suggest that children conceived with ART have increased risks for birth defects compared with their spontaneously conceived counterparts, particularly among singleton infants.

Information on the degree to which certain ART procedures influence the risk of birth defects is limited and often in conclusive. Results from a 2012 cohort study[3] indicated that use of intracytoplasmic sperm injection (ICSI), a procedure in which a single sperm is injected directly into an egg, was associated with increased odds of birth defects relative to spontaneously conceived pregnancies, whereas no effect was noted for conventional in vitro fertilization (IVF) without ICSI. However, pooled risk estimates for the association between birth defects and conventional IVF vs those for the association between birth defects and ICSI have not been found to be markedly different.[6,7]

Similarly, while several studies comparing fresh and frozen-thawed embryo transfers identified similar risks for birth defects regardless of embryo state,[5,9–12] 1 study found an increased prevalence of birth defects for fresh but not frozen embryo cycles when compared with spontaneously conceived births.[3] In addition, results from another study indicated that the odds of blastogenesis defects were 3 times higher for ART births after fresh embryo transfer vs non-ART controls, while no effect was found for frozen-thawed embryo transfers.[13] There is insufficient evidence to evaluate the risk of birth defects following the use of other ART procedures such as assisted hatching[14,15] and donor oocytes[16] or for embryo stage at transfer.[17,18]

Because both ART and birth defects are infrequent events, sufficiently powered studies are needed to evaluate associations, particularly with regard to specific ART procedures. Thus, the aim of our study was to use population-based data from 3 US states to assess the prevalence of birth defects among liveborn infants conceived using ART compared with their non-ART counterparts and to examine the risk of birth defects associated with different types of ART procedures among ART-conceived infants.

Methods

We used data from the States Monitoring ART (SMART) Collaborative, a consortium of participating states and the Centers for Disease Control and Prevention Division of Reproductive Health that promotes state-based surveillance and research on the maternal and child health outcomes of ART.[19] We used linked ART surveillance, birth certificates, and birth defects registry data for Florida, Massachusetts, and Michigan from 2000 to 2010. These states linked their birth defects registry information with birth certificate data and provided deidentified linked data sets to the Centers for Disease Control and Prevention. Then, data from the Centers for Disease Control and Prevention's National ART Surveillance System were linked with the state vital records information using a probabilistic method. Maternal and infant date of birth, plurality, maternal residence zip code, and gravidity (live birth order plus pregnancy losses) were primary linkage variables.[20] Ancillary information such as maternal race/ethnicity, infant sex, and infant birth weight were used to resolve duplicate links. The overall linkage rate was 90.5%.

Key Points

Question

Is assisted reproductive technology associated with an increased risk of birth defects?

Findings

In this cohort study of more than 4 million liveborn infants in 3 states, the prevalence of nonchromosomal birth defects among singleton infants was higher for those conceived using assisted reproductive technology compared with non–assisted reproductive technology singletons. This difference was significant after controlling for maternal characteristics.

Meaning

Infants conceived after assisted reproductive technology had a higher prevalence of certain birth defects; however, this association could be owing to underlying subfertility.

We included all resident live births in Florida, Massachusetts, and Michigan between 2000 and 2010; ART births were those that were successfully linked with the National ART Surveillance System. We excluded births with missing information on plurality and ART births using methods other than transcervical IVF such as gamete intrafallopian transfer and zygote intrafallopian transfer (<1%for all states). The unit of analysis was a liveborn infant. The study was approved by the institutional review boards at the Centers for Disease Control and Prevention, Florida Department of Health, Massachusetts Department of Health, and Michigan Department of Health and Human Services. Informed consent was waived because the research involved no more than minimal risk, the rights and welfare of the subjects were not adversely affected, and the research could not practicably be carried out without such a waiver.

The methods for ascertaining birth defect cases varied by state. The Florida Birth Defects Registry uses passive case-finding methods and ascertains birth defects diagnosed in liveborn infants before 1 year of age. Records are identified from hospital discharge abstracts, the state regional perinatal center database, and the state Children's Medical Services records and are linked to birth certificates. The Massachusetts Birth Defects Monitoring Program uses active case finding whereby birth hospitals and pediatric care facilities submit discharge records with a birth defect diagnosis. Inclusion critera are being a liveborn infant or a fetal death of more than 20 weeks' gestation or weighing more than 350 g, having a structural defect that meets the diagnostic criteria and was diagnosed before 1 year of age, and being born to mothers who were residents of the state at the time of delivery. The Michigan Birth Defects Registry uses passive case ascertainment based on reporting from hospitals, cytogenetic laboratories, and pediatric genetics clinics. Reporting is required for liveborn infants diagnosed with a reportable condition before the second birthday and for fetal deaths after 20 weeks' gestation or more or after they reach 400 g or higher. Michigan data are augmented by information from Children's Special Health Care Services enrollments; confirmed cases are identified as a result of newborn metabolic, hearing, or genetic screening and linked birth and death record information.

Because of differences in case ascertainment across states, we evaluated a limited number of birth defects. We selected defects that were used in previously published national estimates[21,22] because they are usually diagnosed at or immediately after birth and are likely to be consistently collected and reported across different surveillance systems. The

nonchromosomal birth defects assessed in this study were spina bifida with or without anencephaly, encephalocele, anophthalmia and microphthalmia, common truncus, transposition of great arteries, tetralogy of Fallot, atrioventricular septal defects, hypoplastic left heart syndrome, cleft palate without cleft lip, cleft lip with and without cleft palate, esophageal atresia/tracheoesophageal fistula, rectal and large intestinal atresia/stenosis, reduction defects of the upper limbs, reduction defects of the lower limbs, gastroschisis, omphalocele, and diaphragmatic hernia. The chromosomal defects were trisomy 13, trisomy 21 (Down syndrome), and trisomy 18.

We examined the distribution of sociodemographic factors for all ART and non-ART liveborn infants. The variables were derived from the birth certificate and included maternal state of residence, age, race/ethnicity, education, parity (derived from live birth order), tobacco use during pregnancy, diabetes (chronic or gestational), hypertension (chronic or pregnancy-induced), infant plurality, sex of the infant, birth weight, and gestational age. We also compared the prevalence of birth defects for all ART and non-ART births and stratified by singleton and multiple births. For all comparisons, chromosomal defects were stratified by maternal age younger than 35 years and 35 years and older because of known age effects.[23] The prevalence of specific birth defects was reported if the defect was diagnosed in 20 or more infants.

Next, we restricted the study population to ART-conceived infants and evaluated the prevalence of 1 or more nonchromosomal birth defects for certain ART procedures including cycle type (fresh nondonor, fresh donor, frozen-thawed nondonor, or frozen-thawed donor embryos), number of embryos transferred, use of assisted hatching (the purposeful disruption of an embryo's zona pellucida by laser, mechanical, or chemical means), and infertility diagnosis (tubal factor, ovulation disorder, diminished ovarian reserve, endometriosis, male factor, or unexplained infertility). Because information on use of ICSI and day of embryo transfer was only available for fresh embryo cycles, we further restricted the study population to infants resulting from fresh embryo transfer and examined the prevalence of birth defects for all aforementioned procedures and ICSI with male factor infertility, ICSI without male factor infertility, and day of embryo transfer (days 2–3 vs days 5–6). We conducted the analyses for all live births and singleton live births; small numbers precluded evaluation of multiple live births.

We used 2-tailed Satterthwaite-adjusted χ^2 tests to assess differences in the distribution of sociodemographic characteristics for ART vs non-ART liveborn infants. We used multivariable predicted marginal proportions from logistic regression models to compute adjusted risk ratios for the association between use of ART and birth defects. The models were adjusted for maternal age, race/ethnicity, education, parity, smoking during pregnancy, diabetes, hypertension, state of residence, and year of birth. We also used predicted marginal proportions to calculate adjusted risk ratios for the association between use of specified ART procedures and nonchromosomal birth defects. Models for births resulting from fresh and frozen-thawed embryo transfers included cycle type, number of embryos transferred, use of assisted hatching, and infertility diagnosis. Models for births resulting from fresh embryo transfers included type of ART (conventional IVF vs ICSI with and without male factor infertility), cycle type, number of embryos transferred, day of transfer, use of assisted

hatching, and infertility diagnosis. Because information on maternal body mass index was not available for Massachusetts during the study period and was only available from autumn 2007 onward for Michigan and March 2004 onward for Florida, we were unable to evaluate this factor as a potential confounder. We applied the Holm-Bonferroni method to the primary and subgroup analyses to account for multiple comparisons and report multiplicity-adjusted *P* values. *P* values less than .05 were considered significant.

All analyses accounted for clustering of infants within a live birth delivery and clustering of sibling births. We used SAS version 9.3 (SAS Institute) and SUDAAN version 11.0 (RTI International) for analysis. Cohort sizes of less than 20 infants were suppressed and complementary suppression was applied.

Results

Between 2000 and 2010, there were 4 618 076 liveborn infants in Florida, Massachusetts, and Michigan; of those infants, 64 861 (1.4%)were conceived using ART. Compared with non-ART infants, those conceived using ART had higher frequencies of multiple births, a birth weight of less than 2500 g and less than 1500 g, and gestational age of less than 37 weeks and less than 32 weeks (Table 1). There was no difference in the distribution of infant sex. Approximately 45.8%(n = 29 736) of ART-conceived infants were born to mothers who were Massachusetts residents, compared with 18.7%(n = 853 165) of non-ART infants. Mothers of ART infants were more likely to be 30 years or older, non-Hispanic white, college graduates, and nulliparous than mothers of non-ART infants. Tobacco use during pregnancy was less common in mothers of ART vs non-ART infants, while diabetes and hypertension were more common in mothers of ART infants.

Among all liveborn infants, the prevalence of 1 or more selected nonchromosomal defects was 59.97 per 10 000(n = 389) for ART infants compared with 48.40 per 10 000 (n = 22 036) for non-ART infants (Table 2). After adjusting for maternal characteristics and year of birth, ART use was associated with an increased risk for nonchromosomal birth defects (adjusted risk ratio [aRR], 1.28; 95%CI, 1.15–1.42). Tracheoesophageal fistula/esophageal atresia (aRR, 1.93; 95% CI, 1.40–2.67), rectal and large intestinal atresia/stenosis (aRR, 2.03; 95%CI, 1.51–2.74), and reduction deformity of the lower limbs (aRR, 2.18; 95%CI, 1.39–3.43) were positively associated with ART use.

Among singleton live born infants, the prevalence of 1 or more selected nonchromosomal defects was 64.88 per 10 000 (n = 218) for ART infants compared with 48.07 per 10 000 (n = 21 251) for non-ART infants, and this association with ART remained significant in the adjusted model (aRR, 1.39; 95%CI, 1.21–1.59) (Table 3). Likewise, the prevalence of tracheoesophageal fistula/esophageal atresia (aRR, 1.90; 95% CI, 1.23–2.94) and rectal and large intestinal atresia/stenosis (aRR, 1.88; 95% CI, 1.26–282) was higher for ART births vs non-ART births. For women younger than 35 years, the prevalence of Down syndrome was higher for ART vs non-ART births (aRR, 1.63; 95% CI, 1.05–2.54), but the association was not significant after accounting for multiple comparisons (*P* = .18). For women 35 years and older, the prevalence of chromosomal defects was lower for ART births than non-ART births (aRR, 0.66; 95%CI, 0.49–0.88). With the exception of increased risk for rectal and large

intestinal atresia/stenosis (aRR, 2.39; 95% CI, 1.38–4.12), no significant associations with ART were observed for multiple births.

When the study population was restricted to ART births conceived by fresh or frozen embryo transfer, no significant associations between ART procedures and risk of 1 or more nonchromosomal birth defects were detected (Table 4). After further restriction to ART births conceived by fresh embryo transfer, diagnosis of ovulation disorder was marginally associated with nonchromosomal defects among all live births (aRR, 1.53; 95% CI, 1.13–2.06; $P = .05$) (Table 5). The prevalence of nonchromosomal defects was also increased for all live births (aRR, 1.32; 95% CI, 1.02–1.71) and singleton live births where assisted hatching was used (aRR, 1.55; 95% CI, 1.10–2.19); however, the multiplicity-adjusted P values were >.05.

Discussion

Using data from a national ART surveillance system linked with vital records and information from 3 state-based birth defects registries, we found that ART use was associated with an increased risk for certain birth defects. These findings confirm previous reports based on smaller populations[3–5] and provide additional information on variations in risk according to the type of ART procedure used. While we did not find considerable differences in risk by procedure type, the prevalence of nonchromosomal defects was higher for ART births where assisted hatching was used compared with ART births without the technique; however, the association was not statistically significant after accounting for multiple comparisons. Two studies that assessed the risk of birth defects following assisted hatching did not detect an effect[14,15]; however, such an association is plausible because the procedure could damage the embryo and is often used for patients with a poor prognosis who may have other risks for adverse birth outcomes.[24] In addition, we observed a marginally increased prevalence of nonchromosomal defects among births to women with an ovulation disorder, a finding that may be associated with high rates of obesity, a known risk factor for birth defects,[25] among women with polycystic ovary syndrome.[26] While we adjusted for diabetes in our models, it is possible that undiagnosed diabetes among obese women with polycystic ovary syndrome may partially explain this association.

Overall, the prevalence of the selected birth defects in our study population is consistent with national estimates.[22] However, because we used a limited group of conditions, our prevalence estimates of 1% are lower than national estimates for all types of birth defects (approximately 3%).[27] In accordance with other studies,[3–5,7,28–32] we found that the risk of birth defects following ART varied by type of defect; the largest relative risks were observed for gastrointestinal and limb reduction defects. We also found an association between ART use and transposition of great vessels, which has been previously reported.[33] The consistency of our results with those of other studies and meta-analyses that assessed a broader group of birth defects suggests that the excess risk observed in our study is robust. The apparent negative association between ART and Down syndrome in women 35 years or older is probably because of the use of preimplantation genetic screening among older women, primarily for aneuploidy.[34] Notably, in women younger than 35 years, we found increased prevalence of Down syndrome among ART singleton infants compared with non-

ART singletons. The reason for this association is unknown but may be caused by different attitudes toward pregnancy termination in younger women undergoing ART compared with women of the same age with spontaneous conceptions. Overall, older women tend to be more likely than younger women to terminate a pregnancy following a Down syndrome diagnosis[35]; thus, there may be additional factors among younger women using ART that influence their opinions on termination. It is also possible that younger women with an ART-conceived pregnancy were less willing to undergo chorionic villus sampling or amniocentesis because of heightened concerns about risks to the fetus, leading to differences in the rates of prenatal diagnosis and consequent terminations. Another potential explanation is that young women undergoing ART have more serious underlying health issues than older women and thus have poorer-quality embryos.

We did not find a significantly higher prevalence of selected nonchromosomal birth defects in ART births where ICSI was used vs those where conventional IVF was used after adjusting for patient and treatment characteristics. While this finding corroborates the results of meta-analyses published in 2012 and 2013,[6,7] our study did not include genitourinary defects, specifically, hypospadias and cryptorchidism, which are most often implicated in studies of ICSI and birth defects and which may be related to severe male factor infertility.[36,37] Similarly, we did not find an association between birth defects and use of donor oocytes or embryo stage at transfer; however, association with the transfer of 2 or more fresh embryos approached significance, particularly for singleton live births, suggesting that singletons originating from pregnancies where multiple embryos implanted may have increased risks for birth defects. Notably, the presence of a vanishing twin has been identified as a risk factor for small for gestational age in singleton births after IVF.[38]

The primary strength of our study is the use of a large population- and registry-based cohort with accurate information on ART procedures. To our knowledge, this is the largest US study of birth defects and ART to date. Furthermore, we limited our analysis to birth defects that are apparent at birth and thus likely to be reliably ascertained across different states. However, our findings have several limitations. First, we did not have information on the occurrence of birth defects among fetal deaths or pregnancy terminations. As such, our prevalence estimates almost certainly understate the true prevalence of the birth defects included in our study. This may also result in risk ratios that are biased toward or away from the null,[39] depending on the extent to which mothers of ART infants are more or less likely than mothers of non-ART infants to have a miscarriage or terminate a pregnancy affected by birth defects. It is also possible that differences in case ascertainment across states influenced the combined prevalence estimates. Assisted reproductive technology–conceived infants may be monitored more closely, thus resulting in increased detection of birth defects in those infants compared with the general population. Because of variations among states in the collection of information on maternal body mass index, we were unable to control for this potential confounder. Finally, some of the birth certificate variables used in the adjustment are under- reported and may be differentially reported among ART and non-ART groups.

Conclusions

We found that ART use conferred an increased risk for nonchromosomal birth defects, particularly those affecting the gastrointestinal and musculoskeletal systems; however, we were unable to evaluate the potential effect of underlying subfertility on this association. Among ART births, no single procedure was found to substantially increase risk, although use of assisted hatching and diagnosis of ovulation disorders were associated with marginal increases in the prevalence of birth defects. In total, these findings suggest that factors related to subfertility may explain the association between use of ART and birth defects, although additional studies on specific ART procedures are needed. As use of ART continues to increase, careful evaluation of the long-term outcomes of children conceived using these technologies becomes increasingly important. These findings provide additional information on risks of ART that can be used when counselling patients.

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Table 1

Characteristics of Liveborn Infants by Mode of Conception in Florida, Massachusetts, and Michigan, 2000–2010

	No. (%)[b]	
Characteristic[a]	**ART (n = 64 861)**	**Non-ART (n = 4 553 215)**
Plurality		
Singleton	33 601 (51.8)	4 421 154 (97.1)
Twins	28 031 (43.2)	127 013 (2.8)
Triplets/higher	3229 (5.0)	5048 (0.1)
Infant sex		
Male	33 213 (51.2)	2 331 340 (51.2)
Female	31 648 (48.8)	2 221 767 (48.8)
Birth weight, g		
<2500	20 843 (32.2)	357 027 (7.8)
<1500	4172 (6.4)	66 580 (1.5)
Gestational age, wk		
<37	23 456 (36.3)	444 005 (9.8)
<32	4742 (7.3)	74 063 (1.6)
State of residence		
Florida	21 636 (33.4)	2 333 367 (51.2)
Massachusetts	29 736 (45.8)	853 165 (18.7)
Michigan	13 489 (20.8)	1 366 683 (30.0)
Maternal age, y		
<30	7480 (11.5)	2 742 518 (60.2)
30–34	22 587 (34.8)	1 120 673 (24.6)
35–37	15 228 (23.5)	411 713 (9.0)
38–40	10 821 (16.7)	202 982 (4.5)
≥41	8745 (13.5)	75 161 (1.7)
Race/ethnicity		
Non-Hispanic white	52 636 (81.4)	2 651 395 (58.4)
Non-Hispanic black	2629 (4.1)	823 410 (18.1)
Hispanic	648 (1.0)	58 761 (1.3)
Asian/Pacific Islander	5598 (8.7)	838 398 (18.5)
Other/mixed	3159 (4.9)	165 831 (3.7)
Maternal education, y		
<12	883 (1.4)	794 055 (17.6)
12	7788 (12.1)	1 378 011 (30.5)
Some college	13 767 (21.3)	1 121 534 (24.8)
College graduate	42 051 (65.2)	1 217 657 (27.0)

Characteristic[a]	No. (%)[b]	
	ART (n = 64 861)	Non-ART (n = 4 553 215)
Parity		
Nulliparous	42 697 (66.1)	1 906 727 (42.0)
Multiparous	21 884 (33.9)	2 628 451 (58.0)
Tobacco use during pregnancy[c]	806 (1.2)	463 004 (10.2)
Diabetes[d]	4501 (7.0)	184 442 (4.1)
Hypertension[e]	6386 (9.8)	232 898 (5.1)

Abbreviation: ART, assisted reproductive technology.

[a] Missing data less than 1% for all variables.

[b] $P < .01$ for all comparisons between ART births and non-ART births except for infant sex. *P* values account for clustering of infants within a live birth delivery and clustering of sibling births and were adjusted using the Holm-Bonferroni method.

[c] Includes women who smoked during the pregnancy but quit for 2004 to 2010 Florida data and 2010 Michigan data.

[d] Includes chronic and gestational diabetes.

[e] Includes chronic and pregnancy-induced hypertension.

Table 2

Prevalence and Risk Ratios for Selected Birth Defects by Mode of Conception Among Liveborn Infants in Florida, Massachusetts, and Michigan, 2000–2010

	ART (n = 64 861)		Non-ART (n = 4 553 215)			
	No.	Prevalence per 10 000	No.	Prevalence per 10 000	aRR (95% CI)[a]	*P* Value[b]
≥ 1 Nonchromosomal defects[c]	389	59.97	22 036	48.40	1.28 (1.15–1.42)	<.001
Spina bifida with or without anencephaly	22	3.39	1640	3.60	1.47 (0.94–2.29)	.65
Transposition of great vessels	35	5.40	2068	4.54	1.20 (0.85–1.70)	>.99
Tetralogy of Fallot	45	6.94	2165	4.76	1.34 (0.99–1.82)	.51
Atrioventricular septal defect	41	6.32	2068	4.54	0.94 (0.68–1.30)	>.99
Cleft palate only	41	6.32	2577	5.66	1.11 (0.81–1.52)	>.99
Cleft lip and/or cleft palate	46	7.09	3702	8.13	0.97 (0.72–1.30)	>.99
Tracheoesophageal fistula/esophageal atresia	41	6.32	1093	2.40	1.93 (1.40–2.67)	.001
Rectal and large intestinal atresia/stenosis	52	8.02	1893	4.16	2.03 (1.51–2.74)	<.001
Reduction deformity, upper limbs	21	3.24	1049	2.30	1.41 (0.90–2.19)	.79
Reduction deformity, lower limbs	22	3.39	756	1.66	2.18 (1.39–3.43)	.007
≥ 1 Chromosomal defects, <35 y[d]	36	11.97	3715	9.62	1.27 (0.90–1.78)	.85
Down syndrome, maternal age <35 y	35	11.64	3136	8.12	1.39 (0.98–1.96)	.51
≥ 1 Chromosomal defects, ≥35 y	79	22.71	2936	42.56	0.61 (0.48–0.76)	<.001
Down syndrome, maternal age ≥35 y	74	21.27	2603	37.73	0.63 (0.49–0.80)	.001

Abbreviations: aRR, adjusted risk ratio; ART, assisted reproductive technology.

[a] Adjusted for maternal age, race/ethnicity, education, parity, smoking during pregnancy, diabetes (chronic or gestational), hypertension (chronic or gestational), state of residence, and year of birth. Regression models account for clustering of infants within a live birth delivery and clustering of sibling births.

[b] *P* values adjusted using the Holm-Bonferroni method.

[c] Nonchromosomal defects include spina bifida with or without anencephaly, encephalocele, anophthalmia/microphthalmia, common truncus, transposition of great arteries, tetralogy of Fallot, atrioventricular septal defects, hypoplastic left heart syndrome, cleft palate without cleft lip, cleft lip with and without cleft palate, esophageal atresia/tracheoesophageal fistula, rectal and large intestinal atresia/stenosis, reduction defects of the upper limbs, reduction defects of the lower limbs, gastroschisis, omphalocele, and diaphragmatic hernia. Individual defects are presented only if n≥20.

[d] Chromosomal defects include trisomy 13, trisomy 21 (Down syndrome), and trisomy 18. Individual defects are presented only if n≥20.

Table 3

Prevalence and Risk Ratios for Selected Birth Defects by Mode of Conception and Plurality in Florida, Massachusetts, and Michigan, 2000–2010

	No.	ART (per 10 000)	No.	Non-ART (per 10 000)	aRR (95% CI)[a]	*P* Value[b]
Singleton live births						
≥ 1 Nonchromosomal defects[c]	218	64.88	21251	48.07	1.39 (1.21–1.59)	<.001
Spina bifida with and without anencephaly	<20[d]	NA	<20[d]	NA	NA	NA
Transposition of great vessels	25	7.44	2017	4.56	1.63 (1.08–2.46)	.14
Tetralogy of Fallot	25	7.44	2061	4.66	1.47 (0.98–2.20)	.30
Atrioventricular septal defect	26	7.74	2007	4.54	1.10 (0.74–1.63)	.87
Cleft palate only	26	7.74	2497	5.65	1.35 (0.91–2.00)	.41
Cleft lip and/or cleft palate	28	8.33	3579	8.10	1.16 (0.80–1.69)	.87
Tracheoesophageal fistula/esophageal atresia	21	6.25	1028	2.33	1.90 (1.23–2.94)	.04
Rectal and large intestinal atresia/stenosis	25	7.44	1823	4.12	1.88 (1.26–2.82)	.02
Reduction deformity, upper limbs	<20[d]	NA	<20[d]	NA	NA	NA
Reduction deformity, lower limbs	<20[d]	NA	<20[d]	NA	NA	NA
≥ 1 Chromosomal defects, <35 y	20	13.76	3624	9.65	1.45 (0.93–2.26)	.39
Down syndrome, maternal age <35 y	20	13.76	3058	8.14	1.63 (1.05–2.54)	.18
≥ 1 Chromosomal defects, ≥35 y[e]	48	25.18	2854	42.95	0.66 (0.49–0.88)	.04
Down syndrome, maternal age ≥35 y	46	24.13	2532	38.11	0.69 (0.51–0.93)	.13
Multiple live births[f]						
≥ 1 Nonchromosomal defects[c]	171	54.70	785	59.44	1.05 (0.87–1.27)	>.99
Spina bifida with and without anencephaly	<20[d]	NA	<20[d]	NA	NA	NA
Transposition of great vessels	<20[d]	NA	<20[d]	NA	NA	NA
Tetralogy of Fallot	20	6.40	104	7.88	0.89 (0.51–1.55)	>.99
Atrioventricular septal defect	<20[d]	NA	<20[d]	NA	NA	NA
Cleft palate only	<20[d]	NA	<20[d]	NA	NA	NA
Cleft lip with and without cleft palate	<20[d]	NA	<20[d]	NA	NA	NA

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	No.	ART (per 10 000)	No.	Non-ART (per 10 000)	aRR (95% CI)[a]	*P* Value[b]
Tracheoesophageal fistula/esophageal atresia	20	6.40	65	4.92	1.42 (0.82–2.48)	<.99
Rectal and large intestinal atresia/stenosis	27	8.64	70	5.30	2.39 (1.38–4.12)	.01
Reduction deformity, upper limbs	<20[d]	NA	<20[d]	NA	NA	NA
Reduction deformity, lower limbs	<20[d]	NA	<20[d]	NA	NA	NA
≥ 1 Chromosomal defects, <35 y	<20[d]	NA	<20[d]	NA	NA	NA
Down syndrome, maternal age <35 y	<20[d]	NA	<20[d]	NA	NA	NA
≥ 1 Chromosomal defects, ≥35 y[e]	31	19.71	82	32.30	0.61 (0.38–0.96)	.19
Down syndrome, maternal age ≥35 y	28	17.80	71	27.97	0.64 (0.40–1.04)	.41

Abbreviations: aRR, adjusted risk ratio; ART, assisted reproductive technology; NA, not applicable.

[a] Adjusted for maternal age, race/ethnicity, education, parity, smoking during pregnancy, diabetes (chronic or gestational), hypertension (chronic or gestational), state of residence, and year of birth. Regression models account for clustering of births among mothers.

[b] *P* values adjusted using the Holm-Bonferroni method.

[c] Nonchromosomal defects include spina bifida with or without anencephaly, encephalocele, anophthalmia/microphthalmia, common truncus, transposition of great arteries, tetralogy of Fallot, atrioventricular septal defects, hypoplastic left heart syndrome, cleft palate without cleft lip, cleft lip with and without cleft palate, esophageal atresia/tracheoesophageal fistula, rectal and large intestinal atresia/stenosis, reduction defects of the upper limbs, reduction defects of the lower limbs, gastroschisis, omphalocele, and diaphragmatic hernia. Individual defects are presented only if n≥20.

[d] n <20, cell suppressed with complementary suppression.

[e] Chromosomal defects include trisomy 13, trisomy 21 (Down syndrome), and trisomy 18. Individual defects are presented only if n≥20.

[f] Adjusted for maternal age, race/ethnicity, education, parity, smoking during pregnancy, diabetes (chronic or gestational), hypertension (chronic or gestational), state of residence, and year of birth. Regression models account for clustering of infants within a live birth delivery and clustering of births among mothers.

Table 4

Association Between Assisted Reproductive Technology Treatment Characteristics and Having 1 or More Selected Nonchromosomal Birth Defects Among Live born Infants Following Fresh and Frozen Embryo Transfer, Florida, Massachusetts, and Michigan, 2000–2010

	All Live Births			Singleton Live Births Only		
	Prevalence per 10 000	Adjusted RR (95% CI)[a]	*P* Value[b]	Prevalence per 10 000	Adjusted RR (95% CI)[c]	*P* Value[b]
Cycle type						
Fresh nondonor	61.10	1 [Reference]		61.81	1 [Reference]	
Fresh donor	48.38	0.72 (0.46–1.14)	>.99	73.46	1.06 (0.62–1.81)	>.99
Frozen nondonor	53.41	0.66 (0.30–1.45)		56.31	0.76 (0.30–1.92)	
Frozen donor	64.89	0.99 (0.71–1.40)		79.69	1.20 (0.80–1.80)	
No. embryos transferred						
1	51.22	1 [Reference]	>.99	47.63	1 [Reference]	>.99
≥2	60.48	0.99 (0.61–1.58)		66.80	1.12 (0.67–1.86)	
Assisted hatching						
No	56.33	1 [Reference]	.91	58.60	1 [Reference]	.42
Yes	69.61	1.21 (0.96–1.52)		79.95	1.35 (1.00–1.83)	
Diagnosis						
No tubal factor	60.29	1 [Reference]	>.99	63.23	1 [Reference]	>.99
Tubal factor	58.66	0.98 (0.73–1.32)		71.90	1.09 (0.75–1.60)	
No ovulation disorder	56.82	1 [Reference]	.34	63.14	1 [Reference]	>.99
Ovulation disorder	78.54	1.35 (1.02–1.80)		75.79	1.26 (0.85–1.86)	
No diminished ovarian reserve	59.17	1 [Reference]	>.99	61.94	1 [Reference]	>.99
Diminished ovarian reserve	64.70	1.28 (0.88–1.87)		82.24	1.27 (0.79–2.03)	

	All Live Births			Singleton Live Births Only		
	Prevalence per 10 000	Adjusted RR (95% CI)[a]	*P* Value[b]	Prevalence per 10 000	Adjusted RR (95% CI)[c]	*P* Value[b]
No endometriosis	61.56	1 [Reference]	>.99	66.11	1 [Reference]	>.99
Endometriosis	49.90	0.83 (0.59–1.17)		56.70	0.85 (0.55–1.30)	
No male factor	58.89	1 [Reference]	>.99	66.85	1 [Reference]	>.99
Male factor	61.73	1.01 (0.80–1.30)		61.74	0.93 (0.68–1.27)	
No unexplained infertility	59.41	1 [Reference]	>.99	64.65	1 [Reference]	>.99
Unexplained infertility	63.74	1.15 (0.79–1.67)		66.36	1.23 (0.77–1.96)	

Abbreviation: RR, risk ratio.

[a] Adjusted for all variables in the table and maternal age, race/ethnicity, education, parity, smoking during pregnancy, diabetes (chronic or gestational), hypertension (chronic or gestational), state of residence, and year of birth. Regression models account for clustering of infants within a live birth delivery and clustering of births among mothers.

[b] *P* values adjusted using the Holm-Bonferroni method.

[c] Adjusted for all variables in the table and maternal age, race/ethnicity, education, parity, smoking during pregnancy, diabetes (chronic or gestational), hypertension (chronic or gestational), state of residence, and year of birth. Regression models account for clustering of births among mothers.

Table 5

Association Between ART Treatment Characteristics and Having 1 or More Selected Nonchromosomal Birth Defects Among Liveborn Infants Following Fresh Embryo Transfer in Florida, Massachusetts, and Michigan, 2000–2010

	All Live Births			Singleton Live Births Only		
	Prevalence per 10 000	Adjusted RR (95% CI)[a]	*P* Value[b]	Prevalence per 10 000	Adjusted RR (95% CI)[c]	*P* Value[b]
Type of ART						
Conventional IVF	52.57	1 [Reference]		55.67	1 [Reference]	
ICSI with male factor	66.14	1.21 (0.91–1.61)	>.99	64.62	1.10 (0.72–1.67)	>.99
ICSI with no male factor	62.22	1.04 (0.76–1.42)		73.57	1.14 (0.76–1.72)	
Cycle type						
Nondonor	61.1	1 [Reference]		61.81	1 [Reference]	
Donor	48.38	0.74 (0.46–1.19)	>.99	73.46	1.22 (0.70–2.12)	>.99
No. of embryos transferred						
1	32.34	1 [Reference]		26.32	1 [Reference]	
≥2	60.98	1.68 (0.86–3.26)	.89	66.8	1.97 (0.92–4.22)	.71
Day of transfer						
Days 2–3	60.16	1 [Reference]		63.11	1 [Reference]	
Days 5–6	57.3	1.06 (0.80–1.40)	>.99	63.4	1.18 (0.80–1.74)	>.99
Assisted hatching						
No	55.27	1 [Reference]		56.39	1 [Reference]	
Yes	72.26	1.32 (1.02–1.71)	.32	80.67	1.55 (1.10–2.19)	.12
Diagnosis						
No tubal factor	60.47	1 [Reference]	>.99	63.27	1 [Reference]	>.99

	All Live Births			Singleton Live Births Only		
	Prevalence per 10 000	Adjusted RR (95% CI)[a]	*P* Value[b]	Prevalence per 10 000	Adjusted RR (95% CI)[c]	*P* Value[b]
Tubal factor	55.81	1.01 (0.74–1.38)		62.01	0.96 (0.62–1.50)	
No ovulation disorder	55.79	1 [Reference]	.05	60.16	1 [Reference]	>.99
Ovulation disorder	82.35	1.53 (1.13–2.06)		81.73	1.39 (0.91–2.14)	
No diminished ovarian reserve	58.92	1 [Reference]	>.99	60.57	1 [Reference]	>.99
Diminished ovarian reserve	63.38	1.31 (0.88–1.94)		77.61	1.12 (0.67–1.87)	
No endometriosis	61.31	1 [Reference]	>.99	64.64	1 [Reference]	>.99
Endometriosis	48.71	0.77 (0.53–1.13)		52.54	0.77 (0.47–1.25)	
No unexplained infertility	58.99	1 [Reference]	0.86	62.66	1 [Reference]	>.99
Unexplained infertility	63.25	1.36 (0.93–1.99)		65.29	1.41 (0.85–2.33)	

Abbreviations: ART, assisted reproductive technology; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection; RR, risk ratio.

[a] Adjusted for all variables in the table and maternal age, race/ethnicity, education, parity, smoking during pregnancy, drinking during pregnancy, diabetes (chronic or gestational), hypertension (chronic or gestational), state of residence, and year of birth. Regression models account for clustering of infants within a live birth delivery and clustering of births among mothers.

[b] *P* values adjusted using the Holm-Bonferroni method.

[c] Adjusted for all variables in the table and maternal age, race/ethnicity, education, parity, smoking during pregnancy, drinking during pregnancy, diabetes (chronic or gestational), hypertension (chronic or gestational), state of residence, and year of birth. Regression models account for clustering of births among mothers.