Journal of Assisted Reproduction and Genetics (2021) 38:835–846
https://doi.org/10.1007/s10815-021-02095-3

ASSISTED REPRODUCTION TECHNOLOGIES

Risks of nonchromosomal birth defects, small-for-gestational age birthweight, and prematurity with in vitro fertilization: effect of number of embryos transferred and plurality at conception versus at birth

Barbara Luke[1] · Morton B. Brown[2] · Ethan Wantman[3] · Nina E. Forestieri[4] · Marilyn L. Browne[5,6] · Sarah C. Fisher[5] · Mahsa M. Yazdy[7] · Mary K. Ethen[7] · Mark A. Canfield[8] · Hazel B. Nichols[9] · Sergio Oehninger[10] · Kevin J. Doody[11] · Alastair G. Sutcliffe[12] · Carrie Williams[12] · Michael L. Eisenberg[13] · Valerie L. Baker[14] · Caitlin R. Sacha[15] · Philip J. Lupo[16]

Received: 2 December 2020 / Accepted: 27 January 2021 / Published online: 5 February 2021

Abstract

Purpose Excess embryos transferred (ET) (> plurality at birth) and fetal heartbeats (FHB) at 6 weeks' gestation are associated with reductions in birthweight and gestation, but prior studies have been limited by small sample sizes and limited IVF data. This analysis evaluated associations between excess ET, excess FHB, and adverse perinatal outcomes, including the risk of nonchromosomal birth defects.

Methods Live births conceived via IVF from Massachusetts, New York, North Carolina, and Texas included 138,435 children born 2004–2013 (Texas), 2004–2016 (Massachusetts and North Carolina), and 2004–2017 (New York) were classified by ET and FHB. Major birth defects were reported by statewide registries within the first year of life. Logistic regression was used to estimate adjusted odds ratios (AORs) and 95% CIs of the risks of a major nonchromosomal birth defect, small-for-gestational age birthweight (SGA), low birthweight (LBW), and preterm birth (≤36 weeks), by excess ET, and excess ET + excess FHB, by plurality at birth (singletons and twins).

Results In singletons with [2 ET, FHB =1] and [≥3 ET, FHB=1], risks [AOR (95% CI)] were increased, respectively, for major nonchromosomal birth defects [1.13 (1.00–1.27) and 1.18 (1.00–1.38)], SGA [1.10 (1.03–1.17) and 1.15 (1.05–1.26)], LBW [1.09 (1.02–1.13) and 1.17 (1.07–1.27)], and preterm birth [1.06 (1.00–1.12) and 1.14 (1.06–1.23)]. With excess ET + excess FHB, risks of all adverse outcomes except major nonchromosomal birth defects increased further for both singletons and twins.

Conclusion Excess embryos transferred are associated with increased risks for nonchromosomal birth defects, reduced birthweight, and prematurity in IVF-conceived births.

Keywords In vitro fertilization (IVF) · Assisted reproductive technology (ART) · Birth defects · Embryos transferred · Fetal heartbeats · Vanishing twin syndrome

Introduction

As assisted reproductive technology (ART) and in vitro fertilization (IVF) therapy have continued to evolve, there has been a steady decline in the number of embryos transferred (ET), with a resultant fall in the number of multiple births. In the USA, the proportion of IVF cycles with a single embryo transferred has increased from about 10% in 2004 to 40% in 2016, but the multiple birth rate with IVF is still almost 20% [1, 2]. Consequently, there continues to be many IVF cycles that have more than one embryo transferred and, as a result, may be conceived as twins or higher-order multiples, with a proportion experiencing embryonic or fetal loss to result in a singleton at birth. The effects of excess ET and excess fetal heartbeats (FHB, greater than plurality at birth) on perinatal and early childhood outcomes have been evaluated, including birthweight, length of gestation, NICU admission, infant mortality, and neurologic sequelae, but many prior studies have

✉ Barbara Luke
lukeb@msu.edu

Extended author information available on the last page of the article

been limited by small sample sizes, limited or lack of data on IVF treatment parameters, did not evaluate birth defect risks among the survivors, or did not use registry-confirmed data on birth defects [3–12].

Our prior analyses have shown that early fetal losses in both singleton and twin IVF-conceived pregnancies were associated with lowered birthweights and shortened gestations [13, 14]. Even in analyses restricted to women with fresh embryo transfers who had additional embryos cryopreserved during the same cycle and plurality at conception was the same as at birth, the transfer of excess embryos had a stepwise adverse effect on birthweight-for-gestation [15]. Prior analyses also indicated that factors associated with transferring a higher number of embryos reflected suboptimal maternal conditions, less favorable oocyte or embryo quality, less favorable prognosis, or unsuccessful prior cycles [16]. Transferring ≥3 embryos versus 1–2 embryos was significantly more likely with the use of ICSI or assisted hatching and was fourfold more likely with thawed versus fresh embryos and with embryos which were cleavage-stage versus blastocyst-stage [16]. The purpose of this analysis was to evaluate the risk of nonchromosomal birth defects, growth restriction, and prematurity as a function of number of ET and FHB at 6-week gestation based on the linkage of the Society for Assisted Reproductive Technology Clinic Outcome Reporting System (SART CORS) to birth certificates and birth defects registries in four US States.

Methods

This study linked data from the Society for Assisted Reproductive Technology national IVF database, the SART CORS, in four States (New York, Texas, Massachusetts, and North Carolina) to birth certificates and birth defects registries. Data from birth certificates (2004–2013) were collected in our prior study of the risk of childhood cancer and ART [17]. 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 the highest number of annual IVF births in the USA, respectively, in 2016, accounting for 3.0%, 1.5%, 4.7%, and 1.4% of all births in each State [18, 19].

SART CORS data

The SART CORS contains comprehensive information on procedures from more than 83% of all clinics providing IVF and more than 92% of all IVF 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) [20]. The Society makes data available for research purposes to entities that have agreed to comply with SART research guidelines. Patients undergoing treatment 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. 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 4% (in reference 20, Appendix A: Technical Notes, Validation of ART Data, page 525). This study was conducted with the support of SART and was funded by the National Institutes of Health.

Linkage procedure

This study linked IVF cycles reported to the SART CORS from January 1, 2004, to December 31, 2016, that resulted in live births (2004–2013 in Texas, 2004–2016 in Massachusetts and North Carolina, and 2004–2017 in New York) to birth certificates and birth defects registries in all four study States. Initially, study States linked the SART CORS data and birth certificates. Each State received a SART CORS file with identifiers for women with IVF cycles resulting in a live birth who were residents of that State. The States linked the SART CORS data to birth certificate data; >90% of the IVF-conceived births were linked to their respective birth certificates. Each child was then linked to their respective State birth defect registry. The linked files were de-identified before being sent to the investigators and then linked to IVF treatment parameters from the SART CORS by the investigators using 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 their review dated November 13, 2015.

Data exclusions

Birth records with gestational age less than 22 weeks or birth weights less than 300 g were excluded because such births are considered nonviable. Because IVF is rare for a mother younger than 18 years of age, we did not request to include parents aged less than 18 years in the study; therefore, those with ages

less than 18 years were excluded. Cycles were limited to those in which five or fewer embryos were transferred, in accord with the most recent American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Practice Committees recommendations [21]. Live births were limited to singletons and twins. There were a small number of pregnancies with embryo splitting (433 sets of liveborn twins when one embryo was transferred); this number was too few to fit models reliably and was therefore excluded. Data on fetal losses or stillbirths was not available from study States.

Birth defects

The four States participating in this project are current or former 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 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 (Supplemental Table 1) [22]. 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 Supplemental Table 1. We then classified individuals with major birth defects as either "chromosomal" (presence of a major chromosomal defect with or without any other major defect) or "nonchromosomal" (i.e., presence of a major defect but having no chromosomal defect). We present both types of birth defects in eTable 1 in the Supplement, but we limited subsequent analyses to the probability of major nonchromosomal defects only as the relationship between chromosomal birth defects would not be expected to vary by number of ET or FHB.

Race and ethnicity

Maternal race and ethnicity were obtained from the birth certificate; maternal race and ethnicity were also the assigned race of the infant, a rule that was initiated in 1989 by the National Center for Health Statistics. Classification of race and ethnicity was either self-reported by the mother after delivery or by the birth registrar in the birthing facility and reported to the State vital records, as per the local and State policy. Race and ethnicity were included as a factor in this study because of known associations with perinatal outcomes, including birthweight, length of gestation, and birth defects.

Groups

Data on IVF cycles resulting in live births to women who were residents of the study States were categorized into four groups based on the number of embryos transferred (ET) and the number of fetal heartbeats (FHB) at the 6-week ultrasound exam, by plurality at birth. For singleton births, [ET=1, FHB=1] was defined as the reference group; [ET=2, FHB=1] and [ET=3, FHB=1] were the excess embryos transferred groups; and [ET≥2, FHB≥2] was the excess embryos transferred and excess fetal heartbeats group. For twin births, [ET=2, FHB=2] was defined as the reference group; [ET=3, FHB=2] and [ET≥4, FHB=2] were the excess embryos transferred groups; and [ET≥3, FHB≥3] was the excess embryos transferred and excess fetal heartbeats group.

Independent variables

Independent variables were selected a priori for inclusion in the models based on established associations with birth defects and/or adverse outcomes following IVF. These included maternal age at delivery (grouped as 18–29, 30–34, 35–37, 38–40, 41–43, and ≥44 years), race (white, black, Asian, other/missing), Hispanic ethnicity, oocyte source (autologous or donor), embryo state (fresh or thawed), infant sex, and State and year of birth. IVF factors and treatment parameters included infertility diagnoses (male factor, endometriosis, ovulation disorders, diminished ovarian reserve, tubal ligation, other tubal factors, uterine factor, unexplained, other-RFA [reason for ART-immunologic, chromosomal, or other serious disease], and noninfertile [single woman or same-sex partners]); number of diagnoses (one, two or more, or missing); sperm source (partner, donor, mixed, or missing); use of assisted hatching (AZH) and ICSI, which is only available for fresh IVF cycles; oocyte source (autologous or donor); and embryo state (fresh or thawed). Data on day of transfer (to classify embryos transferred as cleavage stage, days 2–3, or blastocyst stage, days 5–6) were only available for live births resulting from the use of autologous oocytes and fresh embryos.

Dependent variables

Birthweight was modeled both as continuous and categorical variables (low birthweight, LBW, <2500 g, and LBW

at term, ≥37-week gestation). Birthweight *Z*-score, as a measure of adequacy of weight for age, was calculated as [actual-reference/standard deviation for the reference population], as recommended by Land [23], using sex-specific national standards [24]. Birthweights of singletons at each gestational age are normally distributed, with a reference mean of zero (0) and a standard deviation of one (1). A birthweight *Z*-score (or standard deviation score) is the deviation of the value for an individual from the mean value of the reference population of singleton births divided by the standard deviation for the reference population. *Z*-scores have a direct relationship with percentiles, with *Z*-scores from −1 to +1 representing 68% of the population distribution, and a *Z*-score of zero equal to the 50th percentile for singleton births. The *Z*-score is useful to describe how far the observed birthweight for gestation is from the expected value. Birthweight Z-score was modeled both as continuous and categorical variables, with *Z*-scores of ≤−1.28 categorized as small-for-gestational age (SGA) for singletons and twins, using the singleton birthweight reference. Length of gestation was modeled as both continuous and categorical variables (<28 weeks, 28–32 weeks, 33–36 weeks, and ≥37 weeks); early preterm birth was defined as ≤32 weeks and preterm birth as ≤36 weeks.

Statistical analyses

Data from each State were processed to generate a common dataset. Because most independent variables were categorized, missing values were included as a separate category; cases with missing values in the dependent variable were not included in the analysis of that variable. Logistic regression was used to estimate adjusted odds ratios (AORs) and 95% confidence intervals (CIs) of the risks of a major nonchromosomal birth defect, small-for-gestational age (SGA) birthweight, low birthweight (LBW, <2500 g) and LBW at term, early preterm birth, preterm birth by excess ET, and excess ET + excess FHB, separately by plurality at birth (singletons and twins). We also repeated the analysis of SGA, LBW, and prematurity after including the presence/absence of a major birth defect as an additional covariate. A general linear model (GLM) was used to model the effect of excess ET, and excess ET + excess FHB on birthweight, birthweight *Z*-score, and length of gestation, separately by plurality at birth. Similar to the logistic models, the GLM models were repeated after including the presence/absence of a major defect. All analyses were performed using SAS Version 9.4 software. We could not properly account for correlation within twin pairs because data were not consistently provided to identify both twins in a pair.

Results

The final study population included 138,435 children (81,673 singletons and 56,762 twins); 6.7% of singleton births began as multiples (93.3% as singletons); and 3.8% of twin births began as triplets or higher order multiples (96.2% as twins). The description of the study population is shown in Table 1. The infertility diagnoses and treatment parameters are shown in Table 2. Compared to the reference groups ([ET=1, FHB=1] for singletons at birth and [ET=2, FHB=2] for twins at birth), women with excess ET and excess ET + excess FHB were more likely to be older and to have cleavage-stage embryos transferred; otherwise, they did not differ substantially by other characteristics, diagnoses, or treatments. Within each plurality, the rate of major nonchromosomal birth defects and the proportions of SGA, early preterm birth, preterm birth, and LBW at term increased with excess ET and excess ET + excess FHB. Of the excess ET groups, 74% of singletons with ET≥3 and FHB=1 had 3 ET; 81% of twins with ET≥4 and FHB=2 had 4 ET.

The results of the logistic regression models are presented in Table 3. The risk of a major nonchromosomal birth defect increased with excess ET, of borderline significance with 2ET and ≥3 ET for singletons. The risk of SGA increased with excess ET, significantly with 2 ET and ≥3 ET in singletons, and with 3 ET in twins. With both excess ET + excess FHB, these risks increased further for both pluralities. A similar pattern was seen for LBW, preterm, and early preterm birth, for both pluralities. The risk of LBW at term was significant with [ET ≥2 and FHB ≥2] in singleton births and [ET=3 and FHB =2] and [ET≥3 and FHB ≥3] in twin births.

The results of the GLM models are shown in Table 4. Length of gestation was decreased significantly with ≥3 ET in singletons and ≥4 ET in twins. With both excess ET + excess FHB, length of gestation was further reduced for both pluralities. Birthweight was reduced with 2 ET and ≥3 ET in singletons and ≥4 ET in twins, and with both excess ET + excess FHB, birthweight was further reduced in both pluralities. Birthweight *Z*-score was significantly reduced with ≥3 ET in singletons and 3 ET in twins, and with both excess ET + excess FHB, birthweight z-score was further reduced for both pluralities.

The use of thawed versus fresh embryos was associated with significantly decreased risks of SGA, LBW, and LBW at term in singletons and twins, with AORs ranging from 0.56 to 0.81 (Supplemental Table 2). The use of donor versus autologous oocytes was associated with significantly increased risks of LBW, and preterm and early preterm birth in singletons and twins, with AORs ranging from 1.22 to 1.44 (Supplemental Table 2). Oocyte source and embryo state combinations were not associated with an increased risk of major nonchromosomal birth defects in singletons or twins.

Table 1 Description of the study population

		Singletons at birth				Twins at birth			
		Reference group*	Excess ET			Reference group*	Excess ET		
					Excess FHB				Excess FHB
Embryos transferred (ET)		1	2	≥3	>1	2	3	≥4	>2
Fetal heartbeats (FHB)		1	1	1	≥2	2	2	2	≥3
N, children		23,753	38,019	14,464	5437	42,851	9008	2720	2183
Maternal age (%)	Mean years ± SD	35.5 ± 5.1	35.4 ± 5.0	37.7 ± 4.2	36.7 ± 4.9	34.7 ± 5.2	36.3 ± 4.4	38.2 ± 4.1	36.6 ± 4.2
	18–29	9.6	10.5	3.9	7.1	13.9	6.5	3.3	4.4
	30–34	36.0	35.1	17.5	27.0	40.2	25.2	14.6	25.0
	35–37	23.5	24.4	21.3	23.3	21.8	27.4	18.3	28.0
	38–40	14.8	16.1	30.6	22.6	11.1	27.2	32.3	26.5
	41–43	8.8	7.4	21.7	12.7	5.8	9.1	26.4	12.1
	≥44	7.3	6.5	5.1	7.4	7.2	4.7	5.1	3.9
Race of mother (%)	White	78.7	79.8	81.1	80.8	80.8	80.9	78.8	80.9
	Black	4.9	6.5	6.6	6.7	6.1	6.8	8.6	6.1
	Asian	13.8	10.6	9.6	9.9	9.8	9.5	9.9	11.7
	Other/missing	2.5	3.1	2.8	2.6	3.2	2.8	2.7	1.2
Ethnicity of mother (%)	Hispanic	7.2	9.4	8.3	8.4	10.8	10.3	12.1	11.1
Mother's BMI (%)	12–24	64.1	57.8	57.7	58.6	58.9	57.9	56.3	61.0
	25–29	21.7	24.4	23.8	23.3	23.8	24.3	26.4	21.1
	30–59	14.3	17.8	18.4	18.1	17.3	17.7	17.3	17.9
	Missing	12.3	20.5	30.0	22.7	21.4	36.3	41.8	40.3
Hypertension**	%	7.9	8.2	8.1	8.3	15.2	13.7	14.2	15.9
Diabetes**	%	7.8	7.6	8.3	7.9	9.0	9.3	10.4	9.9
Infant male sex	%	52.7	51.2	50.5	50.9	51.2	50.7	49.4	50.3
Birthweight	Grams, mean (SD)	3324 ± 586	3277 ± 611	3259 ± 613	3122 ± 681	2374 ± 595	2388 ± 589	2362 ± 588	2254 ± 616
Major birth defect	Rate***	237.4	258.0	257.9	253.8	341.4	351.9	327.2	329.8
Nonchromosomal		228.6	241.5	232.3	235.4	324.8	321.9	286.8	311.5
Chromosomal		8.8	16.6	25.6	18.4	16.6	30.0	40.4	18.3
Small-for-gestational age birthweight****	%	7.0	8.1	8.5	11.5	19.8	22.1	21.9	25.8
Large-for-gestation birthweight****	%	10.1	9.8	10.0	7.8	1.6	1.7	0.9	1.7
Low birthweight (LBW) (<2500 g)	%	7.2	8.4	8.6	13.8	54.7	53.5	55.9	63.0
Length of gestation (%)	Weeks, mean (SD)	38.6 ± 2.1	38.4 ± 2.2	38.3 ± 2.2	38 ± 2.7	35.3 ± 3	35.4 ± 2.9	35.3 ± 2.9	34.9 ± 3
	<28 weeks	0.6	0.8	0.7	1.6	3.3	2.8	3.0	3.0
	28–32 weeks	1.4	1.7	1.7	2.8	10.3	9.7	9.8	15.1
	33–36 weeks	8.0	8.9	9.5	10.9	45.9	44.1	46.1	44.1
	≥37 weeks	90.1	88.6	88.1	84.8	40.5	43.4	41.1	37.7
LBW at term (≥37 weeks, <2500 g)	%	2.2	2.5	2.6	4.3	23.9	24.9	25.0	28.7

*Reference group, ET=1 and FHB=1 for singletons at birth and ET=2 and FHB=2 for twins at birth

**Pregestational (chronic) or gestational

***Rate per 10,000 children

****Small-for-gestational age birthweight is defined as a birthweight *Z*-score ≤−1.28; large-for-gestation birthweight is defined as a birthweight *Z*-score ≥1.28

Table 2 Infertility diagnoses and treatment parameters

		Singletons at birth				Twins at birth			
		Reference group*	Excess ET			Reference group*	Excess ET		
					Excess FHB				Excess FHB
Embryos transferred (ET)		1	2	≥3	>1	2	3	≥4	>2
Fetal heartbeats (FHB)		1	1	1	≥2	2	2	2	≥3
N, children		23,753	38,019	14,464	5437	42,851	9008	2720	2183
Infertility	Male factor	32.5	35.4	35.3	33.9	35.4	37.0	34.3	36.2
Diagnoses (%)	Endometriosis	7.6	10.6	11.6	10.6	10.2	12.9	11.3	11.4
	Ovulation disorders	15.3	16.1	11.8	15.2	17.7	13.4	11.5	13.4
	Diminished ovarian reserve	22.5	20.8	26.5	23.7	20.3	21.1	28.0	23.3
	Tubal ligation	0.9	1.7	2.1	1.7	2.0	1.9	1.9	2.6
	Tubal—other	10.5	12.8	13.9	12.8	12.2	13.0	16.1	13.5
	Uterine factor	4.6	4.5	5.3	5.0	4.5	5.6	6.6	4.8
	Unexplained	18.5	15.5	14.3	15.2	15.2	14.4	14.0	15.4
	Other—RFA**	10.4	9.3	10.4	10.3	9.0	9.8	10.5	9.3
	Noninfertile***	0.8	0.5	0.3	0.6	0.5	0.3	0.1	0.2
Number of diagnoses (%)	One	76.7	74.8	71.5	73.3	75.0	73.4	69.7	73.2
	Two or more	22.3	24.8	28.0	26.1	24.5	26.1	30.2	26.7
	Missing	1.0	0.4	0.4	0.6	0.5	0.5	0.1	0.1
Sperm source (%)	Partner	45.7	70.3	78.8	73.3	75.2	79.4	79.4	80.3
	Mixed	0.1	0.2	0.4	0.2	0.2	0.4	0.7	0.6
	Donor	2.5	3.3	4.5	5.1	3.3	3.5	5.7	4.4
	Missing	51.7	26.2	16.4	21.5	21.3	16.8	14.2	14.6
Assisted hatching (%)	None	61.7	67.1	41.8	62.4	73.6	50.1	33.5	47.5
	Some	0.8	2.7	4.5	3.3	2.4	4.2	6.4	5.7
	All	37.4	30.2	53.7	34.2	24.0	45.6	60.1	46.7
ICSI (%)	None	18.4	22.6	23.0	24.6	5.3	5.3	7.6	5.8
	Some	1.9	5.0	5.1	4.6	48.1	54.7	54.9	54.1
	All	27.8	46.0	55.6	49.3	21.4	16.9	14.2	14.7
	Missing	51.8	26.3	16.4	21.6	25.1	23.1	23.3	25.3
Oocyte	Autologous	87.9	86.6	93.9	85.6	82.5	89.9	92.4	89.4
	Donor	12.1	13.4	6.1	14.4	17.5	10.1	7.6	10.6
Embryo state (%)	Fresh	48.2	73.7	83.6	78.5	78.6	83.2	85.7	85.4
Source (%)	Thawed	51.8	26.3	16.4	21.5	21.4	16.8	14.3	14.6
Day of transfer (%)	Cleavage stage (days 2–3)	16.6	42.1	75.9	46.1	30.2	68.9	80.2	67.2
(Autologous-fresh only)	Blastocyst stage (days 5–6)	81.9	56.3	21.1	52.3	68.4	27.6	14.1	27.2

*Reference group, ET=1 and FHB=1 for singletons at birth and ET=2 and FHB=2 for twins at birth

**Other RFA includes immunologic, chromosomal, or other serious disease

***Noninfertile includes single parent or same sex parents

Day of transfer was only available for children born from autologous oocytes and fresh embryos. Among singleton births from blastocyst-stage embryos with [ET=2 and FHB=1], the risks of SGA and LBW were significantly increased. For singleton births from both cleavage-stage and blastocyst-stage embryos, the risks of SGA, LBW, preterm and early preterm birth, and LBW at term were increased with excess ET + excess FHB, with AORs ranging from 1.39 to 2.50; confidence intervals consistently overlapped between the two groups (cleavage-stage and blastocyst-stage)

Table 3 Risk of adverse outcomes by number of embryos transferred and number of fetal heartbeats

Outcome	ET-FHB groups	Singletons at birth					Twins at birth				
		ET	FHB	Rate**	AOR	95% CI	ET	FHB	Rate**	AOR	95% CI
Major defects***	Reference	1	1	228.6	1.00	Reference	2	2	324.8	1.00	Reference
	Excess ET	2	1	241.5	**1.13**	**1.00, 1.27**	3	2	321.9	1.10	0.95, 1.26
		≥3	1	232.3	**1.18**	**1.00, 1.38**	≥4	2	286.8	1.03	0.81, 1.32
	Excess ET + FHB	≥2	≥2	235.4	1.12	0.92, 1.38	≥3	≥3	311.5	1.09	0.85, 1.41
		ET	FHB	%	AOR	95% CI	ET	FHB	%	AOR	95% CI
Small-for-gestation birthweight	Reference	1	1	7.0	1.00	Reference	2	2	19.8	1.00	Reference
	Excess ET	2	1	8.1	**1.10**	**1.03, 1.17**	3	2	22.1	**1.10**	**1.03, 1.17**
		≥3	1	8.5	**1.15**	**1.05, 1.26**	≥4	2	21.9	1.02	0.92, 1.13
	Excess ET + FHB	≥2	≥2	11.5	**1.62**	**1.46, 1.80**	≥3	≥3	25.8	**1.31**	**1.18, 1.45**
		ET	FHB	%	AOR	95% CI	ET	FHB	%	AOR	95% CI
Low birthweight (<2500 g)	Reference	1	1	7.2	1.00	Reference	2	2	54.7	1.00	Reference
	Excess ET	2	1	8.4	**1.09**	**1.02, 1.16**	3	2	53.5	1.02	0.97, 1.07
		≥3	1	8.6	**1.17**	**1.07, 1.27**	≥4	2	55.9	**1.16**	**1.07, 1.27**
	Excess ET + FHB	≥2	≥2	13.8	**1.91**	**1.73, 2.11**	≥3	≥3	63.0	**1.52**	**1.39, 1.67**
		ET	FHB	%	AOR	95% CI	ET	FHB	%	AOR	95% CI
Preterm birth (≤36 weeks)	Reference	1	1	9.9	1.00	Reference	2	2	59.5	1.00	Reference
	Excess ET	2	1	11.4	**1.06**	**1.00, 1.12**	3	2	56.6	0.97	0.92, 1.02
		≥3	1	11.9	**1.14**	**1.06, 1.23**	≥4	2	58.9	**1.16**	**1.07, 1.27**
	Excess ET + FHB	≥2	≥2	15.2	**1.48**	**1.35, 1.62**	≥3	≥3	62.3	**1.27**	**1.16, 1.39**
		ET	FHB	%	AOR	95% CI	ET	FHB	%	AOR	95% CI
Early preterm birth (≤32 weeks)	Reference	1	1	1.9	1.00	Reference	2	2	13.6	1.00	Reference
	Excess ET	2	1	2.5	**1.16**	**1.02, 1.31**	3	2	12.5	1.00	0.92, 1.07
		≥3	1	2.4	**1.18**	**1.01, 1.39**	≥4	2	12.8	1.11	0.98, 1.25
	Excess ET + FHB	≥2	≥2	4.4	**2.10**	**1.78, 2.49**	≥3	≥3	18.1	**1.60**	**1.42, 1.79**
		ET	FHB	%	AOR	95% CI	ET	FHB	%	AOR	95% CI
Low birthweight (<2500 g) at term (≥37 weeks)	Reference	1	1	2.2	1.00	Reference	2	2	23.9	1.00	Reference
	Excess ET	2	1	2.5	1.03	0.91, 1.17	3	2	24.9	**1.12**	**1.02, 1.22**
		≥3	1	2.6	1.06	0.90, 1.26	≥4	2	25.0	1.12	0.96, 1.31
	Excess ET + FHB	≥2	≥2	4.3	**1.81**	**1.52, 2.17**	≥3	≥3	28.7	**1.35**	**1.15, 1.59**

Models adjusted for number of embryos transferred, number of fetal heartbeats, maternal age, race and Hispanic ethnicity, pregravid BMI, diabetes (pregestational and gestational), oocyte source and embryo state, infant sex, and State and year of birth

**Rate per 10,000 children

***Major defects limited to nonchromosomal only (major birth defects as defined by the National Birth Defects Prevention Network (NBDPN), see Supplemental Table 1)

Bolded values are significantly increased

indicating that the elevated risks did not vary substantially (Supplemental Table 3). A similar pattern was seen with twins (Supplemental Table 4), with elevated risks for SGA, preterm, and early preterm birth for children born from both cleavage-stage and blastocyst-stage embryos, with AORs ranging from 1.22 to 1.66, and confidence intervals consistently overlapping. Twin births from cleavage-stage embryos with [ET=3 and FHB=2] were also at increased risk for preterm birth and LBW at term. Day of transfer with autologous oocytes and fresh embryos was not associated with an increased risk of major nonchromosomal birth defects in singletons or twins.

The effect of the presence of a major nonchromosomal birth defect in singletons and twins was evaluated by including its presence/absence as an additional covariate in the general linear models fitted to length of gestation, birthweight, and birthweight *Z*-score It was associated with a reduction in the length of gestation by 9.90 ± 0.35 days for singletons and 14.39 ± 0.48 days for twins. Since there was an effect on length of gestation, length of gestation and its square were included in the models for birthweight and birthweight *Z*-score. Even after this adjustment, a major nonchromosomal defect was associated with reductions in both these measures

Table 4 The effect of excess embryos transferred and excess fetal heartbeats on length of gestation, birthweight, and birthweight *Z*-score

	ET-FHB groups	Singletons at birth					Twins at birth				
		ET	FHB	Beta	SE	*P* value	ET	FHB	Beta	SE	*P* value
Length of gestation (days)	Excess ET	2	1	−0.20	0.14	0.14	3	2	−0.03	0.25	0.90
		≥3	1	**−0.69**	**0.19**	**0.0002**	≥4	2	**−1.50**	**0.43**	**0.0005**
	Excess ET + FHB	≥2	≥2	**−2.78**	**0.24**	**<.0001**	≥3	≥3	**−3.53**	**0.46**	**<.0001**
Birthweight (g)	Excess ET	2	1	**−15.3**	**5.4**	**0.005**	3	2	−7.0	7.3	0.34
		≥3	1	**−36.3**	**7.3**	**<.0001**	≥4	2	**−47.1**	**12.5**	**0.0002**
	Excess ET + FHB	≥2	≥2	**−163.4**	**9.3**	**<.0001**	≥3	≥3	**−140.4**	**13.3**	**<.0001**
Birthweight *Z*-score	Excess ET	2	1	−0.01	0.01	0.10	3	2	**−0.04**	**0.02**	**0.016**
		≥3	1	**−0.03**	**0.01**	**0.011**	≥4	2	−0.02	0.03	0.45
	Excess ET + FHB	≥2	≥2	**−0.19**	**0.02**	**<.0001**	≥3	≥3	**−0.10**	**0.03**	**0.002**

Models adjusted for number of embryos transferred, number of fetal heartbeats, maternal age, race and Hispanic ethnicity, pregravid BMI, diabetes (pregestational and gestational), oocyte source and embryo state, infant sex, and State and year of birth

Bolded values are significantly increased

(birthweight: 80 ± 10 g in singletons and 90 ± 8 g in twins; *Z*-score 0.17 ± 0.02 and 0.21 ± 0.02).

Discussion

This is one of the first studies to examine the association between the combined factors of number of ET and FHB on the risk of a major nonchromosomal birth defect and other adverse perinatal outcomes in IVF pregnancies. Our analyses indicate that excess ET is associated with increased risks of a major nonchromosomal birth defect in singletons, and SGA, LBW, and preterm birth for singletons and twins. With excess ET + excess FHB, these risks are potentiated, and the risks for early preterm birth and LBW at term increased. These data provide strong support for elective single embryo transfer to optimize the health of IVF offspring and should be considered in counseling patients about the risks versus benefits of transferring more than one embryo.

We also modeled SGA, LBW, and prematurity by including the presence/absence of a major nonchromosomal birth defect as an additional covariate since the presence of a major defect may have resulted in slowed fetal growth and/or the obstetrician's decision to induce an earlier delivery. The adjusted odds ratios of excess ET and excess ET + FHB differed by at most 0.01 from those presented in Table 3, which indicates that the effects of excess ET and excess ET + FHB are independent of the effect of a major nonchromosomal birth defect. The same effects were observed on the outcomes of naturally conceived children [25]. Since infertility status and IVF treatment both appear to contribute to the excess risk of birth defects, they in turn increase the risks for other adverse outcomes, such as SGA, LBW, and prematurity [26].

As noted in the results, the rates of nonchromosomal birth defects, SGA, LBW, and preterm birth were higher when there was excess ET or FHB compared to when there was no excess. Stated in terms of 1000 live IVF births (singleton and twins) which includes a mixture of both excess and no excess births as found in this sample, there are 2.3 and 0.7 more cases, respectively, of major nonchromosomal birth defects than if there were no excess (25.2 instead of 22.9 cases in singletons and 33.2 instead of 32.5 cases in twin children). Similarly, there were 8 and 6 more cases of SGA (78 vs. 70 in singletons and 204 instead of 198 in twins); 10 and 17 more cases of LBW (82 vs. 72 in singletons and 564 vs. 547 in twins); and 8 and 8 more cases of preterm birth (107 vs 99 in singletons and 603 vs 595 in twins).

The occurrence of embryonic or fetal loss with a live birth outcome of the survivor (or survivors) has been known for more than 70 years and systematically studied in early pregnancy with the use of ultrasound. Also known as the vanishing twin syndrome, it has been estimated to occur in more than half of all pregnancies with three or more gestational sacs before the 12th week of gestation [27], and 9–12% of twin conceptions diagnosed by the 8th week of gestation [5–7, 10, 11, 28]. In their analysis of national UK data on IVF-conceived pregnancies, Kamath et al. [29] reported the occurrence of losses between 6–7 weeks and 11–12 weeks in 3.5% of cycles using fresh embryos and 2.4% of cycles using thawed embryos. In our analysis, we found the rate of embryonic or fetal loss to be 6.7% in singleton live births and 3.8% in twin live births.

Our prior analyses of national SART CORS data on 2004–2006 births (23,645 singletons and 14,083 twins) demonstrated a significant residual adverse effect on intrauterine growth from the transfer of multiple embryos, even when plurality at conception was the same as at birth (indicating no embryonic or fetal loss) [15]. Birthweight and birthweight *Z*-score were significantly adversely affected in proportion to the number of embryos transferred, demonstrating a stepwise decrement for both singletons and twins. With embryonic or fetal loss, the risks increased for lowered birthweight, birthweight-for-gestation, and shortened gestation [13, 14, 16]. Our prior results and these current analyses are in accord with other published studies that embryonic or fetal loss is associated with reductions in birthweight and length of gestation [12, 27, 30], as well as increased risks of SGA [11, 12].

We found a reduction in birthweight of 163 g in singletons and 140 g in twins with excess ET + excess FHB, compared to prior reports of singleton birthweight reductions ranging from 89 g [31], 116 g [30], and 178 g [11]; Yan et al. [32] reported reductions of 142.5 g with fresh embryos and 253 g with thawed embryos. In the current study, the risk of SGA in singletons was AOR 1.62 (95% CI 1.46, 1.80), which is in accord with the results of Pinborg et al. [11, 12] (AOR 1.56, 95% CI 1.06, 2.27) and Magnus et al. [30] (AOR 1.48, 95% CI 1.07, 2.03). In the current analyses, the risk of LBW with excess ET + excess FHB was AOR 1.91 (95% CI 1.73, 2.11) in singletons and AOR 1.52 (95% CI 1.39, 1.67) in twins. Prior studies have reported LBW risks (AORs, 95% CIs) in IVF-conceived singletons after a fetal loss ranging from 1.75 (1.36, 2.25) to 2.21 (1.67, 2.65) in fresh embryo cycles and 2.07 (2.12, 3.35) to 2.76 (2.44, 3.13) in thawed embryo cycles [29, 31, 32].

Our analysis showed that length of gestation was reduced with excess ET + excess FHB by 2.78 ± 0.24 days in singletons and 3.53 ± 0.46 days in twins, with risks for preterm and early preterm birth in singletons to be AOR 1.48 (95% CI 1.35, 1.62) and AOR 2.10 (95% CI 1.78, 2.49), respectively. Mansour et al. [6] reported reductions of 0.2 weeks in singletons (37 to 36.8 weeks) and 0.9 weeks in twins (35.2 to 34.3 weeks). The reported risks (AOR, 95% CI) for preterm birth in IVF-conceived singletons after a fetal loss range from 2.41 (1.93, 2.99) to 2.70, (2.37, 3.05) with fresh embryos and 2.13 (1.55, 2.93) to 2.68 (2.15, 3.33) with thawed embryos [29, 32].

The risk of LBW at term, indicating a greater adverse effect on fetal growth than on length of gestation, was evident in the current analyses of excess ET + excess FHB, with risks of AOR 1.81 (95% CI 1.52, 2.17) in singletons and AOR 1.35 (95% CI 1.15, 1.59) in twins. These risks are lower than reported by Petrini et al. [31] of AOR 3.44 (95% CI 2.14, 5.53) for liveborn singletons with an embryonic or fetal loss.

Our analyses indicate in singleton births, even when plurality at conception and at birth is the same, excess ET are associated with a significant progressive increase in adverse outcomes, including major nonchromosomal birth defects, SGA and LBW, and early preterm and preterm birth. In twin births, this effect was less consistent, with significant increases only for SGA, LBW, and preterm birth. Prior research among singleton births with [ET=2 and FHB=1] have reported no significant increased risks for birth defects or SGA [32], or LBW or preterm birth [29].

Placental pathology as a result of excess ET + excess FHB may be an important factor in the pathway for some of these adverse outcomes. In their analysis of a decade of births in Norway, Ebbing et al. [33] reported a prevalence of abnormal umbilical cord insertion to be 7.8% (1.5% velamentous and 6.3% marginal), with conception with ART and twin gestation being the strongest risk factors. Velamentous cord insertion was associated with a greater than twofold increased risk for abruptio placenta and nearly a fourfold increased risk for placenta previa, as well as more than a 50% higher risk of major birth defects. A recent US study of placental pathology in IVF-conceived pregnancies reported that compared to fresh embryo transfers, frozen embryo transfers were associated with an 87% increased risk of marginal cord insertions, nearly fourfold higher risk of subchorionic thrombi, and more than twofold greater risk of fetal vascular malperfusion characteristics with cord anomalies, even with single embryo transfers [34]. This research group also reported that the placentas of singleton births with a vanishing twin were associated with significant altered placental development, including placental weight less than the 10th percentile, velamentous cord insertion, and other anatomic pathologies [35].

Embryo morphology may have been a consideration in the number of embryos to transfer; however, when multiple embryos are transferred, it is unknown which of the transferred embryos resulted in a live birth. In addition, some morphological measures are subjective, such as overall embryo grade, and prior analyses from our group have shown that grades of good and fair give comparable results in terms of live birth, and good morphological progression does not always predict embryo health or subsequent live birth [36].

Few studies have examined the adverse childhood consequences among the survivors of vanishing twin syndrome. Pinborg et al. [11] reported that the later in pregnancy in which a spontaneous reduction occurred, the higher the risk of neurological sequelae. In addition, they reported that the risk of child death was more than threefold greater for the survivor of a vanishing twin pregnancy compared to other singletons (AOR 3.6, 95% CI 1.7, 7.6). It has been hypothesized that a substantial proportion of cerebral palsy may be attributable to the early loss of one conceptus in a twin pregnancy [37], with clinical studies confirming this association [38, 39]. With the continued rise in the use of IVF and ART, the adverse effects of treatment on perinatal and child health should be investigated further [40, 41].

Limitations and strengths

This study has limitations, including lack of data on the duration of infertility prior to treatment, and the inability to determine when in gestation the embryonic or fetal loss occurred; in addition, data on fetal losses or stillbirths were not available from study States. Data on day of transfer (to classify embryos transferred as cleavage stage, days 2–3, or blastocyst stage, days 5–6) were only available for live births resulting from the use of autologous oocytes and fresh embryos. For this study, embryo morphology was not available. The rate of birth defects was limited to live births only, as we did not have any birth defect data on fetal losses or pregnancy terminations for anomalies detected prenatally. The strengths of this study include the large sample size (more than 5000 singleton live births and more than 2100 twin live births with evidence of embryonic or fetal loss), population-based design, and a more contemporary time period than most prior studies (with births through 2017 and birth defects reported through 2018). The four study States include racially and ethnically diverse populations, with high linkage rates, and birth defects registries that utilize similar case definitions. The infertility data and birth defects data were independently collected, minimizing the risk of ascertainment bias. Lastly, we did not rely on the birth certificate for data on infertility treatment or birth defects.

Conclusions

Our analysis indicated that excess ET is associated with increased risks of a major nonchromosomal birth defect, SGA, LBW, preterm, and early preterm birth in singletons, and SGA, LBW, and preterm birth in twins. With excess ET + excess FHB, these risks are potentiated. These adverse outcomes should be considered when determining the appropriate number of embryos to transfer during IVF therapy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10815-021-02095-3.

Acknowledgements The authors thank the Society for Assisted Reproductive Technology and all of its members for providing clinical information to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database for use by patients and researchers. Without the efforts of their members, this research would not have been possible.

Author contribution Drs. Luke and Brown had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Luke and Brown
Acquisition, analysis, or interpretation of data: All authors
Drafting of the manuscript: Luke, Brown
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Brown
Obtained funding: Luke, Brown
Administrative, technical, or material support: All authors
Supervision: Luke

Funding This project was supported by grant R01 HD084377 from the National Institute of Child Health and Human Development National Institutes of Health, USA (Barbara Luke, Principal Investigator).

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.

Declarations

Ethics approval 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.

Conflict of interest Drs. Luke and Brown reported receiving grants from NIH during the conduct of the study. Ms. Forestieri, Dr. Yazdy, and Dr. Browne reported receiving NIH grant support from Michigan State University during the conduct of the study. Mr. Wantman reported receiving personal fees from SART, being a data vendor of SART, and maintaining the SART CORS database during the course of the study; and personal fees from NYU Fertility, MyEggBank, Prelude Fertility, Shady Grove Fertility, Northwell Health Fertility, and Mass General Fertility outside the submitted work. No other disclosures were reported.

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Child Health and Human Development, or the National Institutes of Health, nor any of the State Departments of Health which contributed data.

References

1. Toner J, Coddington CC, Doody K, van Voorhis B, Seifer D, Ball GD, et al. SART & ART in the US: a 2016 update. Fertil Steril. 2016;106(3):541–6.
2. Centers for Disease Control and Prevention. Assisted Reproductive Technology Fertility Clinic Success Rates Report. Atlanta: US Department of Health and Human Services; 2016. p. 2018.
3. Barton SE, Missmer SA, Hornstein MD. Twin pregnancies with a 'vanished' embryo: a higher risk multiple gestation group? Hum Reprod. 2011;26:2750–3.
4. Evron E, Sheiner E, Friger M, Sergienko R, Harlev A. Vanishing twin syndrome: is it associated with adverse perinatal outcome? Fertil Steril. 2015;103:1209–14.
5. La Sala GB, Nucera G, Gallinelli A, Nicoli A, Villani MT, Blickstein I. Lower embryonic loss rates among twin gestations following assisted reproduction. J Assist Reprod Genet. 2005;22:181–4.
6. Mansour R, Serour G, Aboulghar M, Kamal O, Al-Inany H. The impact of vanishing fetuses on the outcome of ICSI pregnancies. Fertil Steril. 2010;94:2430–2.
7. Márton V, Zádori J, Kozinszky Z, Keresztúri A. Prevalences and pregnancy outcome of vanishing twin pregnancies achieved by in vitro fertilization versus natural conception. Fertil Steril. 2016;106:1399–406.

8. Romanski PA, Carusi DA, Farland LV, Missmer SA, Kaser DJ, Walsh BW, et al. Perinatal and peripartum outcomes in vanishing twin pregnancies achieved by in vitro fertilization. Obstet Gynecol. 2018;131:1011–20.
9. Shebl O, Ebner T, Sommergruber M, Sir A, Tews G. Birth weight is lower for survivors of the vanishing twin syndrome: a case-control study. Fertil Steril. 2008;90:310–4.
10. Zhou L, Gao X, Yu W, Zhang Z. Analysis of pregnancy outcomes for survivors of the vanishing twin syndrome after in vitro fertilization and embryo transfer. Eur J Obstet Gynecol Reprod Biol. 2016;203:35–9.
11. Pinborg A, Lidegaard Ø, la Cour FN, Andersen AN. Consequences of vanishing twins in IVF/ICSI pregnancies. Hum Reprod. 2005;20:2821–9.
12. Pinborg A, Lidegaard Ø, la Cour FN, Andersen AN. Vanishing twins: a predictor of small-for-gestational age in IVF singletons. Hum Reprod. 2007;22:2707–14.
13. Luke B, Brown MB, Grainger DA, Stern JE, Klein N, Cedars MI. The effect of early fetal losses on singleton assisted-conception pregnancy outcomes. Fertil Steril. 2009;91:2578–85.
14. Luke B, Brown MB, Grainger DA, Stern JE, Klein N, Cedars MI. The effect of early fetal losses on twin assisted-conception pregnancy outcomes. Fertil Steril. 2009;91:2586–92.
15. Luke B, Brown MB, Stern JE, Grainger DA, Klein N, Cedars M. Effect of embryo transfer number on singleton and twin implantation pregnancy outcomes after assisted reproductive technology. J Reprod Med. 2010;55:387–94.
16. Luke B, Stern JE, Kotelchuck M, Declercq ER, Hornstein MD, Gopal D, et al. Adverse pregnancy outcomes after in vitro fertilization: effect of number of embryos transferred and plurality at conception. Fertil Steril. 2015;104:79–86.
17. Spector LG, Brown MB, Wantman E, Letterie GS, Toner JP, Doody KJ, et al. Risk of childhood cancer after in vitro fertilization in the United States. JAMA Pediatr. 2019;173:e190392. https://doi.org/10.1001/jamapediatrics.2019.0392.
18. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: final data for 2017. In: National vital statistics reports, vol. 67, no. 8. Hyattsville: National Center for Health Statistics; 2018.
19. Sunderam S, Kissin DM, Zhang Y, Folger SG, Boulet SL, Warner L, et al. Assisted reproductive technology surveillance—United States, 2016. Morb Mortal Wkly Rep Surveill Summ. 68(4):1–23.
20. Centers for Disease Control and Prevention. Assisted Reproductive Technology Fertility Clinic Success Rates Report. Atlanta: US Department of Health and Human Services; 2017. p. 2019.
21. Practice Committee of the American Society for Reproductive Medicine and the Practice Committee of the Society for Assisted Reproductive Technology. Guidance on the limits to the number of embryos to transfer: a committee opinion. Fertil Steril. 2017;107:901–3.
22. National Birth Defects Prevention Network (NBDPN). In: Sever LE, editor. Guidelines for conducting birth defects surveillance. Atlanta: National Birth Defects Prevention Network, Inc; 2004.
23. Land JA. How should we report on perinatal outcomes? Hum Reprod. 2006;21:2638–9.
24. Talge NM, Mudd LM, Sikorskii A, Basso O. United States birth weight reference corrected for implausible gestational age estimates. Pediatrics. 2014;133:844–53.
25. Luke B, Brown MB, Wantman E, Forestieri NE, Browne ML, Fisher SC, et al. The risk of birth defects with conception by ART. Hum Reprod. 2020 (in press). https://doi.org/10.1093/humrep/deaa272.
26. Berntsen S, Söderström-Anttila V, Wennerholm UB, Laivuori H, Loft A, Oldereid NB, et al. The health of children conceived by ART: 'the chicken or the egg?'. Hum Reprod Update. 2019;25:137–58.
27. Dickey RP, Taylor SN, Lu PY, Sartor BM, Storment JM, Rye PH, et al. Spontaneous reduction of multiple pregnancy: incidence and effect on outcome. Am J Obstet Gynecol. 2002;186:77–83.
28. Tummers P, De Sutter P, Dhont M. Risk of spontaneous abortion in singleton and twin pregnancies after IVF/ICSI. Hum Reprod. 2003;18:1720–3.
29. Kamath MS, Antonisamy B, Selliah HY, Sunkara SK. Perinatal outcomes of singleton live births with and without vanishing twin following transfer of multiple embryos: analysis of 113,784 singleton live births. Hum Reprod. 2018;33:2018–22.
30. Magnus MC, Ghaderi S, Morker NH, Magnus P, Romundstad LB, Skjærven R, et al. Vanishing twin syndrome among ART singletons and pregnancy outcomes. Hum Reprod. 2017;32:2298–304.
31. Petrini AC, Pereira N, Lekovich JP, Elias RT, Spandorfer SD. Early spontaneous multiple fetal pregnancy reduction is associated with adverse perinatal outcomes in in vitro fertilization cycles. Women Health. 2016;12:420–6.
32. Yan J, Guan Y, Fan H, Mu M, Sun S, Geng W, et al. Neonatal outcomes of singleton live births with vanishing twin syndrome following double embryos transfer in assisted reproductive technology: a retrospective cohort study. J Ovarian Res. 2019;12:67. https://doi.org/10.1186/s13048-019-0539-8.
33. Ebbing C, Kiserud T, Johnsen SL, Albrechtsen S, Rasmussen S. Prevalence, risk factors and outcomes of velamentous and marginal cord insertions: a population-based study of 634,741 pregnancies. PLoS One. 2013;8(7):e70380.
34. Sacha CR, Harris AL, James K, Basnet K, Freret TS, Yeh J, et al. Placental pathology in live births conceived with in vitro fertilization after fresh and frozen embryo transfer. Am J Obstet Gynecol. 2020;222:360.e1–e16.
35. Harris AL, Sacha CR, Basnet KM, James KE, Freret TS, Kaimal AJ, et al. Vanishing twins conceived through fresh in vitro fertilization. Obstet Gynecol. 2020;135:1426–33.
36. Luke B, Brown MB, Stern JE, Jindal SK, Racowsky C, Ball GD. Using the Society for Assisted Reproductive Technology Clinic Outcome System morphological measures to predict live birth after assisted reproductive technology. Fertil Steril. 2014;102(5):1338–44.
37. Pharoah POD, Cooke RWI. A hypothesis for the etiology of spastic cerebral palsy—the vanishing twin. Dev Med Child Neurol. 1997;39:292–6.
38. Glinianaia SV, Pharoah POD, Wright C, Rankin JM, on behalf of the Northern Region Perinatal Mortality Survey Steering Group. Fetal or infant death in twin pregnancy: neurodevelopmental consequence for the survivor. Arch Dis Child Neonatal Ed. 2002;86:F9–F15.
39. Pharoah POD, Price TS, Plomin R. Cerebral palsy in twins: a national study. Arch Dis Child Neonatal Ed. 2002;87:F122–4.
40. Murray E, Fernandes M, Fazel M, Kennedy SH, Villar J, Stein A. Differential effect of intrauterine growth restriction on childhood neurodevelopment: a systematic review. Br J Obstet Gynaecol. 2015;122:1062–72.
41. Mericq V, Martinez-Aguayo A, Uauy R, Iniguez G, Van der Steen M, Hokken-Koelega A. Long-term metabolic risk among children born premature or small for gestational age. Nat Rev Endocrinol. 2017;13:50–62.

Affiliations

Barbara Luke[1] · Morton B. Brown[2] · Ethan Wantman[3] · Nina E. Forestieri[4] · Marilyn L. Browne[5,6] · Sarah C. Fisher[5] · Mahsa M. Yazdy[7] · Mary K. Ethen[7] · Mark A. Canfield[8] · Hazel B. Nichols[9] · Sergio Oehninger[10] · Kevin J. Doody[11] · Alastair G. Sutcliffe[12] · Carrie Williams[12] · Michael L. Eisenberg[13] · Valerie L. Baker[14] · Caitlin R. Sacha[15] · Philip J. Lupo[16]

1 Department of Obstetrics, Gynecology, and Reproductive Biology, College of Human Medicine, Michigan State University, 965 Wilson Road, East Fee Hall, Room 628, East Lansing, MI 48824, USA

2 Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, MI, USA

3 Redshift Technologies, Inc., New York, NY, USA

4 Birth Defects Monitoring Program, State Center for Health Statistics, North Carolina Department of Health and Human Services, Raleigh, NC, USA

5 Birth Defects Research Section, New York State Department of Health, Albany, NY, USA

6 Department of Epidemiology and Biostatistics, School of Public Health, University at Albany, Rensselaer, NY, USA

7 Massachusetts Center for Birth Defects Research and Prevention, Massachusetts Department of Public Health, Boston, MA, USA

8 Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX, USA

9 Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, USA

10 Virginia Beach, USA

11 Center for Assisted Reproduction, Bedford, TX, USA

12 UCL Great Ormond Street Institute of Child Health, University College London, London, UK

13 Division of Male Reproductive Medicine and Surgery, Department of Urology, Stanford University School of Medicine, Palo Alto, CA, USA

14 Division of Reproductive Endocrinology and Infertility, Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA

15 Massachusetts General Hospital Fertility Center and Harvard Medical School, Boston, MA, USA

16 Epidemiology Program, Texas Children's Cancer and Hematology Centers, Baylor College of Medicine, Houston, TX, USA