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Perinatal outcomes among singletons after assisted reproductive technology with single-embryo or double-embryo transfer versus no assisted reproductive technology

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Abstract

Objective: To examine outcomes of singleton pregnancies conceived without assisted reproductive technology (non-ART) compared with singletons conceived with ART by elective single-embryo transfer (eSET), nonelective single-embryo transfer (non-eSET), and double-embryo transfer with the establishment of 1 (DET −1) or ≥2 (DET ≥2) early fetal heartbeats.

Design: Retrospective cohort using linked ART surveillance data and vital records from Florida, Massachusetts, Michigan, and Connecticut.

Setting: Not applicable.

Patient(s): Singleton live-born infants.

Intervention(s): None.

Main Outcome Measure(s): Preterm birth (PTB <37 weeks), very preterm birth (VPTB <32 weeks), small for gestational age birth weight (<10th percentile), low birth weight (LBW <2,500 g), very low birth weight (VLBW <1,500 g), 5-minute Apgar score <7, and neonatal intensive care unit (NICU) admission.

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Result(s): After controlling for maternal characteristics and employing a weighted propensity score approach, we found that singletons conceived after eSET were less likely to have a 5-minute Apgar <7 (adjusted odds ratio [aOR] 0.33; 95% CI, 0.15–0.69) compared with non-ART singletons. There were no differences among outcomes between non-ART and non-eSET infants. We found that PTB, VPTB, LBW, and VLBW were more likely among DET −1 and DET ≥2 compared with non-ART infants, with the odds being higher for DET ≥2 (PTB aOR 1.58; 95% CI, 1.09–2.29; VPTB aOR 2.46; 95% CI, 1.20–5.04; LBW aOR 2.17; 95% CI, 1.24–3.79; VLBW aOR 3.67; 95% CI, 1.38–9.77).

Conclusion(s): Compared with non-ART singletons, singletons born after eSET and non-eSET did not have increased risks whereas DET −1 and DET ≥2 singletons were more likely to have adverse perinatal outcomes.

Keywords

Assisted reproductive technology; double-embryo transfer; elective single-embryo transfer; in vitro fertilization; perinatal outcomes

Several studies have found singletons born to women with infertility after use of assisted reproductive technology (ART) to have worse perinatal outcomes than singletons conceived without ART, even after controlling for potential confounding variables such as maternal age, body mass index (BMI), tobacco use, and parity (1–4). Among ART singletons, risks of growth restriction and preterm birth have been shown to increase with an increasing number of embryos transferred and number of fetal heartbeats established (5–7). Furthermore, there have been studies demonstrating an increased risk of growth restriction and preterm birth after early fetal loss of a co-twin (8, 9).

If adverse outcomes among singleton gestations after ART are partly due to the transfer of more than one embryo or a vanishing twin, we would expect adverse perinatal outcomes among singletons after double-embryo transfer (DET) to be increased compared with singletons in the general population conceived without ART. Furthermore, we would expect singletons born after single-embryo transfer (SET) to be similar to those conceived in the general population without ART. Studies that have compared non-ART to SET infants are limited. Studies from Finland and Sweden have suggested a modest increased risk of preterm birth and low birth weight for singletons born after SET compared with singletons in the general population (10, 11).

Single-embryo transfer can be elective (eSET), defined as the transfer of only one embryo when more than one high-quality embryo is available, or nonelective, the transfer of only one embryo because only one embryo is available. This distinction is important as the nonelective SET group likely represents a population in which the poor response to ovarian stimulation or inability to grow more than one acceptable embryo for transfer may represent an underlying pathology that predisposes these women and their fetuses to worse outcomes. Although the distinction between elective and nonelective SET is not always made in the existing literature, there is some evidence to suggest that eSET singletons also have an increased risk of preterm birth (11, 12) and low birth weight (12) compared with those conceived spontaneously.

We compared perinatal outcomes among singletons born without the use of ART (non-ART) to singletons born after eSET, after single-embryo transfer that was not considered elective (non-eSET), and after DET with the establishment of one early fetal heartbeat (DET −1) or two or more early fetal heartbeats (DET ≥2). We hypothesized that risk of adverse perinatal outcomes will be similar between non-ART and eSET but will increase in a stepwise fashion for each of the following groups: non-eSET, DET −1, and DET ≥2, respectively.

MATERIALS AND METHODS

We performed a retrospective cohort analysis of data from the States Monitoring Assisted Reproductive Technology (SMART) collaborative database that has been described previously elsewhere (13). Briefly, the SMART collaborative was formed to examine ART-related health outcomes in infants and mothers. Data from the National ART Surveillance System (NASS) are linked with states' vital records files and hospital discharge data with a probabilistic linkage methodology using the mother's date of birth, infant's date of birth, plurality, gravidity, and zip code. This method has been validated and found to be both accurate and efficient with a linkage rate of 90.2% for SMART data (13). At the time of this analysis, Connecticut, Florida, Massachusetts, and Michigan were the states included in the SMART database with data ready to analyze. This study was approved by the institutional review boards of the Centers for Disease Control and Prevention (CDC) and the Massachusetts Department of Public Health. The study was reviewed by the Michigan Department of Health and Human Services and was determined not to be human subjects research because all data are deidentified. Connecticut and Florida do not require state-specific institutional review board approval of studies using data contained within the CDC.

All singleton live births in SMART were identified using birth certificates from Connecticut, Florida, Massachusetts, and Michigan between 2000 and 2010. Deliveries were considered non-ART if they could not be linked to the NASS database, suggesting they were not conceived with ART. To minimize confounding, ART deliveries were restricted to fresh, nondonor cycles, and gestational carriers were excluded. All fresh, nondonor cycles were included, regardless of whether preimplantation genetic screening or diagnosis was performed.

We defined eSET as having one embryo transferred and ≥1 embryo cryopreserved from the same cycle as reported in NASS. We compared the demographics among women who delivered a singleton conceived without ART (non-ART) with the women who underwent eSET, non-eSET, DET −1, and DET ≥2 including maternal age, race/ethnicity, tobacco use, history of chronic hypertension, education, marital status, maternal BMI, history of prior live birth, state of delivery, and year of delivery. Demographic variables were obtained from birth certificates and the NASS database for ART deliveries. Because maternal BMI was poorly recorded on birth certificates in Connecticut and was not recorded in Florida before 2005, Michigan before 2008, or Massachusetts before 2011, the BMI data in Table 1 are restricted to Florida and Michigan, 2008 to 2010.

Among ART deliveries we also compared infertility diagnosis, number of prior ART cycles, number of oocytes retrieved, number of embryos cryopreserved, and stage of embryo

transfer. The comparisons of the distribution of these characteristics were made using chi-square and Fisher exact tests. The primary outcomes included preterm birth (<37 weeks), very preterm birth (<32 weeks), small for gestational age (<10 percentile), low birth weight (<2,500 g), very low birth weight (<1,500 g), 5-minute Apgar score <7, and admission to the neonatal intensive care unit (NICU). The NICU admissions were not collected in Connecticut or Massachusetts, and were not collected in Florida and Michigan before 2005. Therefore, the results for admission to the NICU are only among deliveries in Florida and Michigan, 2005 to 2010.

In this study, we employed a weighted propensity score approach to correct for estimation bias (14), which was computed using the type of conception (non-ART, eSET, non-eSET, DET −1, and DET ≥2) as the dependent variable and maternal factors (maternal age, race/ethnicity, tobacco use, education, marital status, and prior live birth) as predictors (15, 16). The weights (inverse of propensity scores) were then used in the multiple logistic regression models. We calculated crude and adjusted odds ratios (aOR) and 95% confidence intervals (CI) for each outcome among ART singletons compared with non-ART singletons adjusting for the weighted scores and other factors, including history of chronic hypertension, state, and year of delivery. Missing values were excluded from analysis because the overall missing rate was <4%.

As previously mentioned, data available for BMI are limited in our database, so we could not use BMI as a confounder in our logistic regression models. Body mass index is a potential confounding variable as obesity has been associated with pregnancy complications that may affect fetal growth and delivery timing (17). To examine the influence of obesity on our results, we performed a subanalysis restricted to the states and years with available BMI data (Florida and Michigan, 2008 to 2010), and performed logistic regression as described earlier with and without BMI added as an additional adjustment factor. The data analysis was performed using SAS 9.3 (SAS Institute) and SUDAAN 11 (RTI International).

RESULTS

There were 4,837,983 live born non-ART singletons and 17,364 live-born singletons conceived by single or double fresh embryo transfer in Connecticut, Florida, Massachusetts, and Michigan between 2000 and 2010. Among the ART singletons, 1,138 were eSET, 1,599 non-eSET, 13,387 DET with 1 early fetal heartbeat (DET −1), and 1,240 DET with ≥2 early fetal heartbeats (DET ≥2). The characteristics by type of conception are presented in Table 1.

Singleton infants born after eSET were less likely to have mothers ≥38 years old (4.9%) compared with non-ART (6.3%), non-eSET (27.9%), DET −1 (15.6%), and DET ≥2 (15.0%) singletons. Women in the non-ART group were more likely to be non-Hispanic Black and Hispanic than women who conceived with any type of ART. They were also more likely to smoke, have completed fewer years of education, and to be unmarried.

Among singleton live births in Florida and Michigan, maternal BMI varied by type of conception, with mothers of 20.5% of non-ART singletons having a BMI of ≥30 kg/m^2

compared with mothers of 11.2% of eSET singletons, mothers of 14.5% of non-eSET singletons, mothers of 15.0% of DET −1 singletons, and mothers of 20.1% of DET ≥2 singletons. Compared with all the ART groups, women who delivered non-ART singletons were more likely to have had a prior live birth. The type of conception varied by state, with Florida contributing the most non-ART births (46.9%) and Massachusetts contributing the majority of ART births (48.3%), including eSET (67.2%) and all other ART singleton groups.

Table 1 also shows infertility diagnosis and characteristics of the ART cycle among ART births. A greater percentage of singleton deliveries after eSET than singleton deliveries from the other ART groups were from a first ART cycle, a cycle with ≥10 oocytes retrieved, and a blastocyst (days 5 to 6) transfer.

Primary outcomes are shown in Table 2. Among non-ART singletons, 395,149 (8.2%) delivered preterm (<37 weeks) compared with 103 (9.1%) of eSET, 144 (9.0%) of non-eSET, 1,493 (11.2%) of DET −1, and 188 (15.2%) of DET ≥2 singletons. Results from the adjusted analyses indicated no difference in the odds of preterm birth or very preterm birth between eSET singletons or non-eSET singletons compared with singletons conceived without ART. The DET −1 and DET ≥2 singletons had greater odds than non-ART singletons of being preterm and very preterm (DET −1 preterm aOR 1.38; 95% CI, 1.16–1.64; very preterm aOR 1.85; 95% CI, 1.30–2.64; DET ≥2 preterm aOR 1.58; 95% CI, 1.09–2.29; very preterm aOR 2.46; 95% CI, 1.20–5.04).

There was no difference in the odds of having a small for gestational age infant for any group of ART singletons compared with non-ART singletons. However, compared with non-ART singletons, an increase in the odds of low birth weight or very low birth weight was detected among DET −1 (aOR 1.59; 95% CI, 1.21–2.12; and aOR 2.64; 95% CI, 1.59–4.41, respectively) and DET ≥2 singletons (aOR 2.17; 95% CI, 1.24–3.79; and aOR 3.67; 95% CI, 1.38–9.77, respectively). The eSET singletons had lower adjusted odds than non-ART singletons of having a 5-minute Apgar score <7 (aOR 0.33; 95% CI, 0.15–0.69).

The outcomes of the subanalysis restricted to deliveries with maternal BMI available (Florida and Michigan, 2008 to 2010), were similar with and without controlling for BMI. Compared with the main analysis including deliveries in all four states for all years, fewer outcomes achieved statistical significance due to small sample size. Among eSET singletons, the only statistically significant outcome was a lower odds of a 5-minute Apgar < 7 when BMI was not included in the model (aOR 0.21; 95% CI, 0.05–0.97); however, this was similar to the odds when BMI was adjusted for (aOR 0.22; 95% CI, 0.05–1.02). The DET −1 singletons had statistically significantly greater odds than non-ART singletons of being very preterm and having a very low birthweight when BMI was adjusted for (very preterm birth aOR 4.32; 95% CI, 1.49–12.59; very low birthweight aOR 5.11; 95% CI, 1.82–14.38) as well as when BMI was not adjusted for (very preterm birth aOR 4.36; 95% CI, 1.51–12.53; very low birthweight aOR 5.16; 95% CI, 1.86–14.32). Results for the other outcomes were similar when BMI was and was not adjusted for, although they failed to reach statistical significance (data not shown).

DISCUSSION

The risks of adverse perinatal outcomes we examined were not statistically significantly increased among singletons born after ART with SET compared with non-ART singletons. Furthermore, eSET singletons were less likely than non-ART singletons to have a 5-minute Apgar score <7. Among all single-embryo transfers, those that are elective likely represent women with optimal maternal conditions (18) who may be less likely to experience a poor perinatal outcome. Although we controlled for many of these maternal characteristics, it is possible there are additional unmeasured factors in women who respond well to ovarian stimulation, grow multiple good-quality embryos, and are candidates for eSET that decreases their risk of a poor perinatal outcome.

Our findings differ from existing studies that found increased risks among eSET singletons compared with singletons conceived without ART. A study including 269 SET singletons in Finland, of which 83% were eSET, found SET singletons had increased risks of cesarean delivery, preterm birth, low birth weight, and 1-minute Apgar score <7 compared with the singletons from the general population (10). A study of infants in Sweden found that, compared with singletons in the general population, the eSET singletons had a statistically significantly higher rate of preterm birth <37 weeks (11). A meta-analysis with two studies —the Finnish study as well as a study from Belgium (12)—found the risk of preterm birth doubled for eSET as compared with spontaneously conceived singletons. Our study differs in several ways that may help to explain these differences. In many of the countries in which these studies were performed SET is the most common type of embryo transfer; in some cases, it is mandated for women of a certain age (7). Therefore, women undergoing eSET are not chosen based on favorable prognostic factors as they often are in the United States. Furthermore, we were able to apply a propensity score method to adjust for factors that influence the probability of receiving ART.

We found increased risks of poor perinatal outcomes among singletons after ART were limited to those conceived after DET. This finding is consistent with several studies that have found an increased risk of growth restriction and preterm birth among singletons conceived by DET (5–7). As hypothesized by DeSutter et al. (7), the presence of a second fetal sac could impact the implantation process of the ongoing “twin” and may thus be the origin of pregnancy complications for the continuing singleton gestation. However, this theory suggests that singletons born after the transfer of one embryo, regardless of whether they were elective or nonelective, would have similar outcomes. We found that although singletons born after nonelective SET had similar odds of adverse perinatal outcomes compared with non-ART singletons, eSET singletons had decreased odds of adverse perinatal outcomes. This may be in part because the nonelective SET group represents a population in which the poor response to ovarian stimulation or inability to grow more than one acceptable embryo for transfer represents an underlying pathology that predisposes these women and their fetuses to worse outcomes compared with women eligible for eSET.

An emerging trend in the literature suggests that the risk for singleton gestations may be proportional to the number of embryos transferred, or number of early fetal heartbeats established. In 2010 Luke et al. (5) found that compared with SET, moderate growth

restriction among singletons was increased by 15%, 23%, and 37%, respectively, with 2, 3, and ≥4 embryos transferred. Likewise, in 2015, Luke et al. (6) found the risk of preterm birth and low birth weight was increased among singletons with >1 fetal heartbeat established compared with those with only 1 early fetal heartbeat. Our findings are consistent with these, showing the risk of preterm birth, low birth weight, and NICU admission to be increased for singletons after DET but not after SET. Moreover, the magnitude of risks was higher for singletons born after DET ≥2 than for DET −1. When comparing both groups with non-ART singletons, singletons born after DET with the establishment of two or more early fetal heartbeats were 1.6 times more likely to have been delivered preterm and 2.5 times more likely to have been born very preterm, while those with the establishment of one early fetal heartbeat were 1.4 times more likely to have been preterm and 1.9 times more likely to have been very preterm. DET ≥2 singletons were 2.2 times more likely and DET −1 singletons were 1.6 times more likely to have low birth weight compared with non-ART singletons. Similarly, DET ≥2 singletons were 3.7 times more likely to have a very low birth weight and DET −1 singletons 2.6 times more likely as compared with the non-ART group.

The strengths of our study include the comprehensive nature of the SMART database with the ability to obtain information on all deliveries in the general population, including both those conceived with and without ART. Because of the breadth of the database, we were able to use a propensity score to adjust for factors that influence the probability of receiving ART. We also were able to control for other important maternal characteristics such as chronic hypertension that could have influenced the likelihood of an adverse outcome.

This study is not without limitations. Inherent to retrospective cohort studies, there is potential for unmeasured confounding, some of which are due to limitations with data availability. Examples include maternal drug use and history of preterm birth, both of which we were unable to measure. History of preterm birth is one of the strongest risk factors for preterm birth in a subsequent pregnancy (19). We also lacked information on multifetal reduction and the rate of unplanned pregnancies in the non-ART group, both of which may influence pregnancy outcomes. Additionally, BMI was not uniformly collected and could not be included in the regression models for our overall outcomes; however, we were able to assess the extent to which BMI may be a confounder by conducting a subanalysis with data from the two states that collected BMI, and the results indicated little to no confounding.

Another variable we were unable to measure was the rate of monozygotic twinning, which has been reported to occur at a twofold to fivefold higher rate for blastocysts versus cleavage-stage embryo transfer (20). It is possible that loss of a monozygotic twin, specifically a monochorionic twin, may adversely impact the surviving co-twin compared with the loss of a dizygotic twin; thus, the stage of embryo transfer may impact our primary outcomes. Even with the use of such a large database, the outcomes were too rare to stratify our results by stage of embryo transfer to assess any potential bias caused by stage of transfer.

Although some of the birth certificate variables used in the adjustment and as a primary outcomes are underreported and may be differentially reported among ART and non-ART

groups, the validity of some of these variables has been studied in various states. The sensitivity of birth certificates has been found to be moderate to excellent for estimated gestational age, low birth weight, preterm birth, Apgar scores, and previous live birth (21–23).

It is possible the underlying infertility of couples seeking ART may increase their risk of adverse perinatal outcomes, independent of ART treatment. Women with subfertility who ultimately conceived without treatment or conceived with fertility medications or intrauterine insemination were included in the non-ART comparison group in our study. We were unable to determine the percentage of pregnancies conceived with fertility treatments other than ART (i.e., intrauterine insemination and fertility medications). We cannot determine whether the increased risks detected were due to the underlying infertility or the ART procedures themselves. However, if the underlying infertility contributed to adverse perinatal outcomes, inclusion of subfertile women in the comparison group would reduce differences rather than exaggerate them.

Finally, we studied a long period of time (2000 to 2010) to obtain an adequate sample size. The practice of ART has evolved since 2000, and the risks over time may have changed. Although the year of delivery was adjusted for in our model, we were unable to analyze trends over time with respect to any of the outcome parameters given the relatively small number of primary outcomes among subgroups annually.

CONCLUSION

Based on our results, there does not appear to be an increased risk of adverse perinatal outcomes for singletons conceived with SET compared with singletons in the general population. The risks for singletons after ART appear to be related to the transfer of >1 embryo, with the highest risk among pregnancies with >1 early fetal heartbeat established that ultimately result in the birth of a singleton. This study adds to the growing body of literature that has indicated that eSET is strongly associated with the ideal pregnancy outcome after ART.

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TABLE 1

Characteristics among singleton live births in Connecticut, Florida, Massachusetts, and Michigan, 2000–2010.

Characteristics	Non-ART n (%)	eSET n (%)	Non-eSET n (%)	DET −1 n (%)	DET ≥2 n (%)	*P* value
Total	4,837,983	1,138	1,599	13,387	1,240	
Age (y)						< .001
<35	4,087,594 (84.5)	838(73.6)	705 (44.1)	7,727 (57.7)	749 (60.4)	
35–37	447,179 (9.2)	244 (21.4)	448 (28.0)	3,574 (26.7)	305 (24.6)	
≥38	303,210 (6.3)	56 (4.9)	446 (27.9)	2,086 (15.6)	186 (15.0)	
Race/ethnicity						< .001
Non-Hispanic White	3,011,046 (62.2)	924(81.2)	1,302 (81.4)	10,836 (80.9)	985 (79.4)	
Non-Hispanic Black	848,792 (17.6)	39 (3.4)	60 (3.8)	567 (4.2)	71 (5.7)	
Hispanic	711,839(14.7)	65 (5.7)	114(7.1)	1,048 (7.8)	109(8.8)	
Other	266,306 (5.5)	110(9.7)	123 (7.7)	936 (7.0)	75(6.1)	
Tobacco use[a]	468,293 (9.7)	27 (2.4)	25(1.6)	267 (2.0)	52 (4.2)	< .001
Chronic hypertension[a]	70,423 (1.5)	15(1.3)	29 (1.8)	223 (1.7)	25 (2.0)	< .001
Education[a]						< .001
< High school	832,296 (17.2)	9(0.8)	12 (0.8)	169 (1.3)	42 (3.4)	
High school	1,448,301 (29.9)	101 (8.9)	179(11.2)	1,637 (12.2)	164(13.2)	
Some college	2,026,856 (41.9)	635 (55.8)	901 (56.4)	7,661 (57.2)	691 (55.7)	
Some graduate	488,506 (10.1)	390 (34.3)	502 (31.4)	3,865 (28.9)	341 (27.5)	
Marital status						< .001
Unmarried	1,873,423 (38.7)	36(3.2)	57 (3.6)	476 (3.6)	106(8.6)	
Married	2,963,658 (61.3)	1,102 (96.8)	1,541 (96.4)	12,911 (96.4)	1,134(91.5)	
Maternal BMI kg/m2[a,b]						< .001
<18.5	41,427 (4.3)	11 (4.4)	10 (4.1)	99 (3.8)	12 (3.3)	
18.5–24.9	442,995 (45.6)	161 (64.7)	143 (59.1)	1,412 (54.3)	190 (52.2)	
25–29.9	230,459 (23.7)	43 (17.3)	43 (17.8)	607 (23.4)	77 (21.2)	
≥R30	199,579 (20.5)	28 (11.2)	35 (14.5)	391 (15.0)	73 (20.1)	
Missing	57,059 (5.9)	6 (2.4)	11 (4.6)	90 (3.5)	12 (3.3)	
History of prior live birth[a]						< .001

Characteristics	Non-ART n (%)	eSET n (%)	Non-eSET n (%)	DET −1 n (%)	DET ≥2 n (%)	*P* value
0	2,032,216 (42.0)	685 (60.2)	999 (62.5)	9,409 (70.3)	781 (63.0)	
1	1,573,307 (32.5)	329 (28.9)	411 (25.7)	2,963 (22.1)	326 (26.3)	
≥2	1,210,901 (25.0)	117 (10.3)	179 (11.2)	967 (7.2)	129 (10.4)	
State of delivery						< .001
Connecticut	418,662 (8.7)	131 (11.5)	180 (11.2)	1,793 (13.4)	129 (10.4)	
Florida	2,270,604 (46.9)	167 (14.7)	341 (21.3)	3,796 (28.4)	314 (25.3)	
Massachusetts	825,186 (17.1)	765 (67.2)	930 (58.2)	6,174 (46.1)	527 (42.5)	
Michigan	1,323,531 (27.4)	75 (6.6)	148 (9.3)	1,624 (12.1)	270 (21.8)	
Among ART deliveries only						
Total		1,138	1,598	13,382	1,240	
Infertility diagnosis (not mutually exclusive)						
Tubal		204 (17.9)	261 (16.3)	2,605 (19.5)	258 (20.8)	.006
Endometriosis		89 (7.8)	206 (12.9)	1,875 (14.0)	169 (13.6)	< .001
Uterine		42 (3.7)	65 (4.1)	427 (3.2)	37 (3.0)	.222
Ovulatory dysfunction		260 (22.9)	197 (12.3)	2,100 (15.7)	229 (18.5)	< .001
Diminished ovarian reserve		26 (2.3)	192 (12.0)	736 (5.5)	78 (6.3)	< .001
Male factor		442 (38.8)	616 (38.5)	5,327 (39.8)	502 (40.5)	.652
Other		130 (11.4)	272 (17.0)	1,696 (12.7)	153 (12.3)	< .001
Unexplained		197 (17.3)	257 (16.1)	2,1443 (16.0)	168 (13.6)	.073
No. of prior ART cycles						< .001
0		858 (75.4)	913 (57.1)	8,550 (63.9)	802 (64.7)	
1		158 (13.9)	316 (19.8)	2,504 (18.7)	215 (17.3)	
≥2		122 (10.7)	370 (23.1)	2,326 (17.4)	223 (18.0)	
Unknown		0	0	7 (0.1)	0	
No. of oocytes retrieved						< .001
0–4		22 (1.9)	503 (31.5)	904 (6.8)	55 (4.4)	
5–9		182 (16.0)	559 (35.0)	3,581 (26.8)	260 (21.0)	
≥10		873 (76.7)	466 (29.1)	8,029 (60.0)	854 (69.0)	
Unknown		61 (5.4)	71 (4.4)	873 (6.5)	71 (5.7)	
No. of embryos cryopreserved						< .001

Characteristics	Non-ART n (%)	eSET n (%)	Non-eSET n (%)	DET −1 n (%)	DET ≥2 n (%)	*P* value
0		-	1,599 (100)	7,122 (53.2)	522 (42.1)	
1–2		400 (35.2)	-	2,359 (17.6)	260 (21.0)	
3–4		320 (28.2)	-	1,790 (13.4)	186 (15.0)	
≥5		418 (36.7)	-	2,105 (15.7)	270 (21.8)	
Unknown		0	0	11 (0.1)	2 (0.2)	
Stage of embryo transfer						
Cleavage (d 2/3)		527 (46.3)	1,124 (70.3)	9,057 (67.7)	688 (55.5)	< .001
Blastocyst (d 5/6)		608 (53.4)	437 (27.3)	4,117 (30.7)	528 (42.6)	
Other		3 (0.3)	38 (2.4)	213 (1.6)	24 (1.9)	

Note: ART = assisted reproduction technology; BMI = body mass index; DET = double-embryo transfer; DET —1 = double-embryo transfer with the establishment of 1 early fetal heartbeat; DET≥2 = double-embryo transfer with the establishment of ≥ 2 early fetal heartbeats; eSET = elective single embryo transfer; OR = odds ratio.

[a]Variable contains missing data; < 2% unless otherwise stated.

[b]Restricted to 2008–2010, Florida and Michigan data only.

TABLE 2

Perinatal outcomes among singleton live births by type of conception in Connecticut, Florida, Massachusetts, and Michigan, 2000–2010.

	Non-ART	eSET			Non-eSET			DET −1			DET ≥2		
Outcome	**n (%)**	**n (%)**	**OR (95% CI)**	**aOR[a] (95% CI)**	**n (%)**	**OR (95% CI)**	**aOR[a] (95% CI)**	**n (%)**	**OR (95% CI)**	**aOR[a] (95% CI)**	**n (%)**	**OR (95% CI)**	**aOR[a] (95% CI)**
Preterm birth <37 wk	395,149 (8.2)	103 (9.1)	1.10 (0.90–1.35)	1.39 (0.82–2.37)	144 (9.0)	1.14 (0.96–1.35)	1.49 (0.92–2.42)	1,493 (11.2)	1.41 (1.34–1.49)[b]	1.38 (1.16–1.64)[b]	188 (15.2)	2.02 (1.73–2.36)[b]	1.58 (1.09–2.29)[b]
Very preterm birth <32 wk	62,773 (1.3)	14 (1.2)	0.92 (0.53–1.57)	0.72 (0.24–2.13)	21 (1.3)	1.05 (0.69–1.60)	2.04 (0.58–7.20)	224 (1.7)	1.34 (1.18–1.53)[b]	1.85 (1.30–2.64)[b]	34 (2.7)	2.29 (1.63–3.22)[b]	2.46 (1.20–5.04)[b]
SGA <10th percentile	450,633 (9.3)	97 (8.5)	0.90 (0.73–1.11)	2.83 (0.83–9.67)	135 (8.4)	0.91 (0.77–1.08)	0.89 (0.44–1.83)	1,208 (9.0)	0.98 (0.93–1.04)	1.03 (0.78–1.35)	136 (11.0)	1.18 (0.99–1.41)	1.14 (0.68–1.89)
LBW <2,500 g	304,227 (6.3)	69 (6.1)	0.93 (0.73–1.19)	1.36 (0.55–3.36)	110 (6.9)	1.12 (0.92–1.35)	1.16 (0.54–2.50)	1,082 (8.1)	1.33 (1.25–1.41)[b]	1.59 (1.21–2.12)[b]	159 (12.8)	2.18 (1.85–2.57)[b]	2.17 (1.24–3.79)[b]
VLBW <1,500 g	55,489 (1.1)	9 (0.8)	0.64 (0.32–1.27)	0.91 (0.20–4.17)	20 (1.3)	1.13 (0.74–1.73)	3.27 (0.66–16.24)	216 (1.6)	1.46 (1.28–1.66)[b]	2.64 (1.59–4.41)[b]	35 (2.8)	2.60 (1.85–3.65)[b]	3.67 (1.38–9.77)[b]
5-min Apgar <7	63,095 (1.3)	12 (1.1)	0.80 (0.45–1.42)	0.33 (0.15–0.69)[b]	31 (1.9)	1.50 (1.06–2.14)[b]	0.58 (0.31–1.09)	144 (1.1)	0.82 (0.70–0.97)[b]	1.17 (0.62–2.19)	22 (1.8)	1.36 (0.89–2.08)	1.85 (0.70–4.89)
Admission to NICU[c]	113,866 (5.7)	15 (6.7)	1.19 (0.71–2.01)	3.20 (0.58–17.62)	32 (9.0)	1.65 (1.15–2.37)[b]	1.23 (0.66–2.30)	293 (7.6)	1.37 (1.22–1.55)[b]	1.47 (0.92–2.34)	51 (10.4)	1.92 (1.44–2.57)[b]	2.07 (0.84–5.09)

Note: A propensity score weight was used for ART infants to correct estimation bias. aOR = adjusted odds ratio; ART = assisted reproduction technology; CI = confidence interval; DET = double-embryo transfer; DET−1 = double embryo transfer with the establishment of 1 early fetal heartbeat; DET≥2 = double embryo transfer with the establishment of ≥ 2 early fetal heartbeats; eSET = elective single-embryo transfer; LBW = low birth weight; NICU = neonatal intensive care unit; OR = odds ratio; SGA = small for gestational age; VLBW = very low birth weight.

[a]Compared with non-ART. Propensity weights created for all infants using the following predictors: maternal age, race/ethnicity, tobacco use, education, marital status, and prior live birth. Adjusted for chronic hypertension, state, and year of delivery.[a] Compared with non-ART. Propensity weights created for all infants using the following predictors: maternal age, race/ethnicity, tobacco use, education, marital status, and prior live birth. Adjusted for chronic hypertension, state, and year of delivery.

[b]Significant outcomes.

[c]Among Florida and Michigan deliveries for years 2005 to 2010 only. Chronic hypertension was not adjusted for due to the small number of mothers who had chronic hypertension and an infant admitted to the NICU.