

Elective transfer of one embryo is associated with a higher cumulative live birth rate and improved perinatal outcomes compared to the transfer of two embryos with in vitro fertilization

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Objective: To compare the effects of initial elective single embryo transfer (ieSET) and initial double embryo transfer (iDET) strategies on the cumulative live birth rate (CLBR) and perinatal outcomes after IVF.

Design: Retrospective cohort study.

Setting: Society for Assisted Reproductive Technology (SART) reporting clinics.

Patient(s): 49,333 patients with initial oocyte retrievals between January 2014 and December 2015.

Intervention(s): None.

Main Outcome Measure(s): The primary outcome was CLBR, defined as up to 1 live birth resulting from a retrieval cycle and linked transfer cycles. Secondary outcomes included cycles to pregnancy, multifetal delivery rate, infant birthweight, and perinatal mortality rate.

Result(s): Compared to iDET, ieSET was associated with increased CLBR (74% vs. 57%; adjusted odds ratio [AOR], 1.32; 95% CI, 1.26–1.38). When stratified by age, the same trend was seen in all age categories, with statistical significance for those <38 years of age. ieSET was associated with reduced multifetal delivery (8% vs. 34%; AOR, 0.13; 95% CI, 0.12–0.14), increased birthweight (mean difference, 406 grams; 95% CI, 387–425), reduced preterm births (1.2% vs. 2.8%), and reduced perinatal mortality (0.5% vs. 1.2%). Compared with iDET, ieSET was associated with slightly more embryo transfer cycles (1.7 vs. 1.4 cycles; AOR, 1.19; 95% CI, 1.16–1.21) to achieve a pregnancy resulting in live birth.

Conclusion(s): The association of ieSET with a higher CLBR and markedly improved perinatal outcomes outweigh the relatively minor increase in time to pregnancy, reinforcing the guidance for eSET in initial transfer cycles, particularly in younger patients with a good prognosis. (*Fertil Steril Rep*® 2021;2:50–7. ©2020 by American Society for Reproductive Medicine.)

Key Words: Elective single embryo transfer, IVF, cumulative live birth rate, SART, perinatal outcomes

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In vitro fertilization (IVF), despite being costly, is a commonly used infertility treatment now accounting for nearly 2% of all births in the

United States (1). In the past, the effectiveness of IVF was measured and reported by the Society for Assisted Reproductive Technology (SART) as

the live birth rate per initiated cycle. These reporting systems emphasized the live birth rates with the initial transfer of fresh embryos and did not associate the contribution of the cohort of non-transferred, cryopreserved embryos to the reproductive potential of an IVF treatment cycle. This may have fueled providers' practice of transferring multiple embryos, both in hopes of increasing live birth rates for their patients and increasing publicly reported clinic live birth rates to achieve a competitive advantage over other

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IVF centers. The resulting high rate of riskier multiple gestation pregnancies has been recognized as a frequent complication of IVF but one that has been accepted and even desired by some patients (2).

Recent changes in IVF practice have led to changes in the way IVF outcomes are tracked and reported. Improvements in embryo cryopreservation techniques, such as vitrification, have resulted in high thawed embryo survival rates, approximately 95% (3, 4) and frozen/thawed embryo live birth rates that are similar to that achieved with fresh embryo transfer (5). As the high risks of multiple gestation pregnancies have been recognized by both providers and patients, elective single embryo transfer (eSET), defined as the transfer of 1 embryo to the uterus when >1 suitable embryo is available, has been recommended and increasingly used in the United States as a means of reducing this complication of IVF. Beginning with cycles in 2014, SART began linking all outcomes of embryo transfers of both fresh and cryopreserved embryos to their treatment cycle of origin. Specifically, the cumulative live birth rate (CLBR), which SART defines as up to 1 live birth resulting from a retrieval cycle and linked transfers cycles, can now be calculated and reported. The CLBR more accurately captures the reproductive potential of an IVF treatment cycle (6). The SART clinic-specific report now emphasizes the cumulative singleton live birth rate per initiated IVF stimulation cycle, a statistic that promotes centers that transfer fewer embryos to reduce multiple gestation pregnancies even if it takes more embryo transfer cycles to achieve a pregnancy resulting in live birth.

A meta-analysis of studies comparing eSET with double embryo transfer (DET) of cleavage stage embryos cultured in vitro for 2 or 3 days concluded that live birth rates were lower with eSET, but similar live birth rates could be achieved after an additional frozen embryo transfer in those receiving eSET (7). Blastocyst embryos cultured for 5–7 days have higher implantation rates and most of the IVF cycles in the United States use this embryo culture technique (8). We have previously reported that as compared with DET, eSET with blastocysts results in slightly lower live birth rates and markedly lower multiple birth rates when evaluating only the first embryo transfer cycle (9). In addition, we found that clinics utilizing higher rates of eSET report similar live birth rates and thus are not at a competitive disadvantage compared with clinics transferring more embryos (9). Despite this, DET still is practiced commonly in US IVF centers.

Prior studies have been shortsighted in evaluating the effect of eSET on the outcomes of the initial transfer cycle. The effect of eSET on the CLBR is unknown. The purpose of this study is to compare the effects of a strategy of initial eSET (ieSET) vs. initial DET (iDET) on CLBR (up to 1 live birth from a retrieval and linked transfer cycles), multiple gestation delivery rate, perinatal outcomes, and time to pregnancy. We hypothesize that patients who have ieSET will have higher CLBR than those who have iDET.

MATERIALS AND METHODS

We obtained de-identified primary IVF clinic data collected by SART for retrospective analysis. Data were collected and

verified by SART and reported to the Centers for Disease Control and Prevention, in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The data in the SART Clinic Outcome Reporting System are validated annually with some clinics having on-site visits for chart review on the basis of an algorithm for clinic selection. During each visit, the data reported by the clinic were compared with information recorded in the patients' charts. Ten out of 11 data fields selected for validation were found to have discrepancy rates of $\leq 5\%$ (10). The project was submitted to the Institution Review Board of the University of Iowa for approval and qualified as exempt, given the de-identified nature of the study (Determination of Human Subjects IRB ID# 201608711).

Study Population

The dataset included patients aged 21 to 45 years who had their first oocyte retrieval between January 2014 and December 2015. Patients who had oocyte or embryo banking cycles or preimplantation genetic testing of embryos were excluded, as were those who did not undergo ieSET or iDET (Supplemental Fig. 1, available online). eSET was defined as the transfer of 1 embryo to the uterus with a least 1 additional embryo cryopreserved. This definition has been used in other studies and allows a comparison when there are 2 embryos available to transfer in each group (11). Therefore, we eliminated patients in whom iSET was nonelective and only 1 viable embryo was available for transfer.

We linked subsequent frozen embryo transfers occurring through December 2016 that used embryos from the initial retrieval to determine the CLBR and multiple gestation rate per oocyte retrieval cycle. Transfer cycles in which embryos from the initial stimulation cycle were mixed with embryos from a subsequent stimulation cycle were excluded ($n = 725$).

Outcomes

The primary outcome was CLBR, defined as up to 1 live birth (including multifetal deliveries) resulting from a retrieval cycle and linked transfers cycles (6). Thus, the patient was censored after conceiving a pregnancy resulting in delivery and later cryopreserved embryo transfers cycles after delivery were not linked. This definition was selected for its clinical meaningfulness as an indicator of the quality and success of IVF outcomes and because it has also been used by SART reporting clinics.

The secondary outcomes included live birth in the first transfer cycle, multifetal delivery, miscarriage, time to pregnancy resulting in live birth, number of cycles to pregnancy, infant birth weight, preterm birth, and perinatal mortality. The time to pregnancy resulting in delivery was calculated for cycles resulting in a live birth by adding 10 days (standard amount of time from embryo transfer to the pregnancy test) to the number of days between medication start in the retrieval cycle and the embryo transfer that resulted in the live birth. The number of treatment cycles to pregnancy was calculated by summing the initial retrieval cycle and all linked subsequent transfer cycles through the cycle resulting in live birth.

TABLE 1

Patient and cycle characteristics	ieSET (n= 17,576)	iDET (n= 31,757) ^a
Age	32.0 ± 3.5	33.6 ± 4.3
Body mass index	25.2 ± 5.5	26.3 ± 6.0
Gravidity	0 (0–1)	0 (0–1)
Parity	0 (0–0)	0 (0–0)
Diagnosis		
Male infertility	4,180 (24%)	6,996 (22%)
Endometriosis	722 (4%)	1,351 (4%)
Polycystic ovaries	2,300 (13%)	3,101 (10%)
Diminished ovarian reserve	565 (3%)	2,531 (8%)
Tubal factor	1,325 (8%)	2,709 (9%)
Uterine factor	252 (1%)	386 (1%)
Unexplained	3,473 (20%)	5,222 (16%)
Multiple	3,712 (21%)	8,000 (25%)
Other	1,047 (6%)	1,461 (5%)
Patient Race		
White	7,829 (71%)	14,712 (68%)
Black	741 (7%)	1,774 (8%)
Hispanic/Latino	611 (6%)	1,990 (9%)
Asian	1,663 (15%)	2,535 (12%)
Other/multiracial	189 (2%)	488 (2%)
Number of 2 pronuclei embryos available	11.3 ± 6.0	8.5 ± 5.52
Number of embryos available	5.90 ± 3.67	4.36 ± 3.15
≥ 3 embryos available for transfer	15,324 (87.2%)	19,063 (60%)
Good quality embryos available	16,016 (91%)	25,042 (79%)
Day >5 transfers	16,746 (95%)	22,219 (70%)
Day <4 transfers	830 (5%)	9,538 (30%)
Assisted hatching	6,403 (36%)	12,896 (41%)
Intracytoplasmic sperm injection	12,114 (70%)	24,138 (77%)
Follicle stimulating hormone dosage	2,596.0 ± 1246.13	3,086.8 ± 1487.0
Initial transfer during fresh cycle	13,225 (75%)	26,777 (84%)
Had ≥ 1 subsequent transfers after initial transfer	7,496 (42.1%)	5,957 (18.8%)
Number of subsequent transfers among those who had subsequent transfers	2 (2, 3)	2 (2, 2)

Note: Values are mean ± SD, medians (interquartile range), or number (%). iDET = initial double embryo transfer; ieSET = initial elective single embryo transfer.
^a P < .001 (iDET vs. ieSET for all values).

Mejia. High cumulative birth rate with eSET. Fertil Steril Rep 2020.

We chose to evaluate time to pregnancy resulting in a live birth rather than just time to live birth to avoid the confounder of preterm deliveries. Preterm birth was examined at 2 levels, with outcome variables for both gestational age at delivery <28 weeks and <32 weeks.

Covariates

The covariates considered included patient's age, body mass index (BMI), race, gravidity, parity, infertility diagnosis, follicle stimulating hormone (FSH) dosage, the use of donor sperm, intracytoplasmic sperm injection (ICSI), total 2 pronuclei embryos (2PN), embryo stage, availability of a good quality embryo for transfer, assisted hatching, ultrasound-guided transfer, and length of follow-up.

Patient age, BMI, gravidity, and parity as reported at the beginning of their stimulation cycle were used for analysis.

BMI was calculated using the reported height and weight. Data entry fields for patient race in the SART database include White, Black, Hispanic/Latino, Asian, American Indian/Alaska native, native Hawaiian/other Pacific Islander, and other. On the basis of the response to this item, we categorized the patients reporting >1 race as multiracial. Because of the low number of patients in the American Indian/Alaska native, native Hawaiian/other Pacific Islander, other, and multiracial groups, these groups were combined into a single category of other/multiracial. The data entry fields for infertility diagnosis included male infertility, endometriosis, polycystic ovaries, diminished ovarian reserve, tubal ligation, tubal hydrosalpinx, tubal other, uterine, and other diagnosis. For our analyses, tubal ligation, tubal hydrosalpinx, and tubal other were combined into a single tubal diagnosis category. We then created a multiple diagnosis category, classifying anyone who had ≥ 2 of the other listed diagnosis categories as having multiple diagnoses.

The FSH dosage was defined as the total number of international units of hormone administered to the female patient during the stimulation cycle. If any eggs within the cohort were fertilized using ICSI, the patient was classified as using ICSI. Embryo stage was classified on the basis of the number of days of embryo culture into blastocyst (5–7 days of culture) or cleavage stage transfer (2–4 days of culture). In the SART data entry form, the embryo grade is defined as the subjective assessment of the overall quality of the embryo as “good,” “fair,” or “poor” on the basis of the assessment of certain characteristics of the embryo such as fragmentation, symmetry, inner cell mass quality, or trophectoderm quality. “Good” quality embryos are described as “embryos free of or with only minor imperfection.” Patients were classified as having a good quality embryo if any linked cycle reported the transfer of at least 1 embryo with a “good” embryo morphology grade. The number of embryos available was calculated by summing the number of embryos transferred and cryopreserved from the initial retrieval cycle. The length of follow-up was classified by the year (2014 or 2015) of the initial ovarian stimulation and oocyte retrieval. Because of the de-identification process, the exact length of follow-up for each patient was not available, so the year of the retrieval cycle was used as a proxy for the length of follow-up. All patients were followed up through 2016.

Missingness

The patient's infertility diagnoses, age, and race, when missing in the index cycle, were backfilled from the first available cycle. Complete case analysis was performed for modeling.

Statistical Analysis

Statistical analyses were performed with SPSS version 26 and SAS 9.4. Student's *t* test, Mann-Whitney *U* test, and chi-square test were used to describe the sample. Generalized linear mixed models were used to assess the impact of clinical and demographic factors on the CLBR, multifetal delivery rate, miscarriage rate, and time to pregnancy. For each

TABLE 2

Cumulative live births in ieSET vs. iDET by age category

Cumulative live births within the full sample

Age categories	ieSET (n = 16,854)	iDET (n = 29,826)	Adjusted OR (95% CI)
All Ages	12,516/16,854 (74%)	17,072/29,826 (57%)	1.32 (1.26–1.38)
Age <35	9,956/12,950 (77%)	10,915/16,896 (65%)	1.31 (1.24–1.39)
Age 35–37	2,054/2,934 (70%)	3,966/7,055 (56%)	1.27 (1.15–1.40)
Age 38–40	459/837 (55%)	1,929/4,444 (43%)	1.06 (0.90–1.24)
Age >40	47/133 (35%)	262/1,431 (18%)	1.36 (0.91–2.04)

Cumulative live births among patients with transfer of a fresh embryo in initial transfer

Age categories	ieSET (n = 12,771)	iDET (n = 25,156)	Adjusted OR (95% CI)
All Ages	9,513/12,771 (74%)	13,926/25,156 (55%)	1.40 (1.33–1.48)
Age <35	7,653/9,951 (77%)	8,754/13,936 (63%)	1.41 (1.32–1.50)
Age 35–37	1,551/2,217 (70%)	3,304/6,056 (55%)	1.34 (1.20–1.50)
Age 38–40	294/542 (54%)	1,652/3,900 (42%)	1.07 (0.88–1.29)
Age >40	15/61 (25%)	216/1,264 (17%)	0.80 (0.42–1.52)

Cumulative live births among patients with transfer of a frozen embryo in initial transfer

Age categories	ieSET (n = 4,083)	iDET (n = 4,670)	Adjusted OR (95% CI)
All Ages	3,003/4,083 (74%)	3,146/4,670 (67%)	1.06 (0.96–1.17)
Age <35	2,303/2,999 (77%)	2,161/2,960 (73%)	1.03 (0.90–1.16)
Age 35–37	503/717 (70%)	662/999 (66%)	1.03 (0.83–1.28)
Age 38–40	165/295 (56%)	277/544 (51%)	0.93 (0.68–1.27)
Age >40	32/72 (44%)	46/167 (28%)	1.59 (0.80–3.13)

Note: Values are numbers (%) or mean \pm SD. CI = confidence interval; iDET = initial double embryo transfer; ieSET = initial elective single embryo transfer; OR = odds ratio. OR is adjusted for age, body mass index, total 2 pronuclei embryos, cleavage vs. blastocyst transfer, availability of good quality embryos, assisted hatching, length of follow-up period, and race.

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TABLE 3

Secondary outcomes by age group in ieSET vs. iDET

Age category	ieSET (n = 16,854)	iDET (n = 29,826)	Adjusted OR (95% CI)
Secondary outcome: Multifetal pregnancy			
Full Sample	959/12,516 (8%)	5,888/17,072 (34%)	0.13 (0.12–0.14)
Age <35	797/9,956 (8%)	4,182/10,915 (38%)	0.14 (0.12–0.17)
Age 35–37	143/2,054 (7%)	1,219/3,966 (31%)	0.10 (0.06–0.16)
Age 38–40	17/459 (4%)	456/1,929 (24%)	0.12 (0.11–0.13)
Age >40	2/47 (4%)	31/262 (12%)	0.31 (0.07–1.39)
Secondary outcome: Miscarriage			
Full Sample	2,163/13,917 (16%)	3,025/19,684 (15%)	1.24 (1.16–1.32)
Age <35	1,518/10,899 (14%)	1,438/12,107 (12%)	1.28 (1.18–1.39)
Age 35–37	459/2,363 (19%)	787/4,650 (17%)	1.29 (1.13–1.48)
Age 38–40	164/586 (28%)	621/2,490 (25%)	1.34 (1.09–1.66)
Age >40	22/69 (32%)	179/437 (41%)	0.82 (0.46–1.47)
Secondary outcome: Time to pregnancy resulting in delivery (d)			
Full Sample	82.3 \pm 100.6	50.8 \pm 72.0	1.47 (1.44–1.50)
Age <35	80.1 \pm 98.0	50.8 \pm 71.2	1.60 (1.53–1.68)
Age 35–37	89.5 \pm 107.4	50.2 \pm 72.2	1.78 (1.62–1.96)
Age 38–40	100.5 \pm 124.0	51.4 \pm 75.1	1.41 (1.38–1.45)
Age >40	91.2 \pm 81.5	53.7 \pm 80.0	1.48 (1.08–2.03)
Secondary outcome: Number of cycles to pregnancy			
Full Sample	1.7 \pm 0.8	1.4 \pm 0.6	1.19 (1.16–1.21)
Age <35	1.7 \pm 0.8	1.4 \pm 0.6	1.22 (1.17–1.27)
Age 35–37	1.7 \pm 0.8	1.3 \pm 0.6	1.32 (1.22–1.43)
Age 38–40	1.8 \pm 0.8	1.3 \pm 0.6	1.17 (1.14–1.19)
Age >40	1.9 \pm 0.6	1.4 \pm 0.6	1.24 (0.97–1.59)

Note: Values are mean \pm SD or number (%) CI = confidence interval; iDET = initial double embryo transfer; ieSET = initial elective single embryo transfer; OR = odds ratio. OR is adjusted for age, body mass index, total 2 pronuclei embryos, cleavage vs. blastocyst transfer, availability of good quality embryos, assisted hatching, length of follow-up period, and race.

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TABLE 4

Infant outcomes among patients with a live birth

Infant outcomes	ieSET	iDET ^a	Mean difference (95% CI)
Number born^b			
1 infant	9,933 (93%)	10,138 (65%)	—
2 infants	717 (7%)	5,297 (34%)	—
3 infants	11 (<1%)	126 (1%)	—
4 infants	0 (0%)	2 (<1%)	—
Birth weight ^c	3,161.5 ± 785.7	2,755.7 ± 840.1	405.8 (387.0–424.6)
Preterm birth before 28 wk ^b	127/10,664 (1.2%)	432/15,565 (2.8%)	—
Preterm birth before 32 wk ^b	322/10,664 (3.0%)	1047/15,565 (6.7%)	—
Perinatal mortality ^c	58/11,080 (0.5%)	259/20,912 (1.2%)	—

Note: The ieSET vs. iDET grouping is on the basis of the patients' initial transfer cycle; the pregnancy that resulted in a live birth may have occurred in a subsequent cycle that may have used elective single embryo transfer, double embryo transfer, or multiple embryo transfer. ieSET = initial elective single embryo transfer; iDET = initial double embryo transfer; CI = confidence interval

^a $P < .001$ (iDET vs. ieSET for all values).

^b Outcomes ($n = 26,299$ pregnancies) are reported per female patient or pregnancy (multiple gestation pregnancies are counted only once). The number born is missing for 75 pregnancies.

^c Outcomes ($n = 32,521$ infants) are reported per infant (each infant from multiple gestation pregnancies is included). Birth weight data are missing for 118 ieSET infants and 212 iDET infants.

Mejia. High cumulative birth rate with eSET. *Fertil Steril Rep* 2020.

outcome variable, the models of all possible predictor subsets were fit, and the top model was selected using the Bayesian information criterion. The variables considered for model selection included infertility diagnosis, total 2PN, ICSI, embryo stage, the availability of a good quality embryo for transfer, the length of follow-up, assisted hatching, donor sperm, ultrasound-guided embryo transfer, gravidity, parity, patient's age, BMI, race, and FSH dosage. The statistical significance of any differences found was tested using a multivariable regression model accounting for differences in important clinical and demographic variables between the populations studied.

A sub analysis to confirm the trends seen in the whole sample was completed by stratifying patients by ages <35, 35–37, 38–40, and >40 years. Additional sub analyses were performed stratified by type (fresh and frozen) of initial transfer. A final sub analysis examined CLBRs of patients who had ieSET and underwent either eSET or DET in a second transfer cycle.

RESULTS

Nearly twice as many patients had iDET compared to ieSET in this study group. [Supplemental Figure 1](#) includes the details of those excluded and total population included for analysis. Patients who had ieSET were younger and had a lower BMI, gravidity, and parity than patients who had iDET ([Table 1](#)). Overall, infertility diagnoses were similar between the groups, although more women in the iDET group had the diagnosis of diminished ovarian reserve (8% vs. 3%, $P < .001$), which was reflected by a lower mean \pm SD antimüllerian hormone level in these patients (3.7 ± 3.5 vs. 4.9 ± 4.4 , $P < .001$).

There were differences in cycle characteristics when comparing the ieSET and iDET groups ([Table 1](#)). Women having ieSET had more number of 2PN embryos; a higher percentage of women had blastocyst-stage embryo transfers, and many had good quality embryos available for transfer. Cycles in the ieSET group had a lower total FSH dosage and

used assisted hatching and ICSI less frequently than those in the iDET group.

When accounting for a woman's age, race, BMI, the total number of 2PN, cleavage versus blastocyst-stage transfers, the availability of a good quality embryo, the use of assisted hatching, and the length of follow-up, ieSET was associated with a significantly higher CLBR in the full sample of patients (74% vs. 57%; adjusted odds ratio [AOR], 1.32; 95% CI, 1.26–1.38). When stratifying the groups by a woman's age, there was a higher CLBR in the ieSET group in all age categories, although the difference was statistically significant only for women <38 years of age ([Table 2](#)). Next, we compared ieSET vs. iDET in only those who had a fresh embryo transfer and the same increased CLBR with ieSET was seen (74% vs. 55%; AOR, 1.40; 95% CI, 1.33–1.48). In addition, we compared ieSET vs. iDET among patients who had a “freeze all” cycle whose initial transfer was frozen, and a similar increased CLBR trend was seen, although the difference was no longer statistically significant (74% vs. 67%; AOR, 1.06; 95% CI, 0.96–1.17). The results of fresh and frozen subsample analyses stratified by age followed similar trends for CLBR as those seen in the full sample ([Table 2](#)).

The use of ieSET was associated with a significantly lower multifetal delivery rate in the full sample (8% vs. 34%; AOR, 0.13; 95% CI, 0.12–0.14). When stratifying groups by age, ieSET was associated with a significantly lower multifetal delivery rate in all age categories other than women >40 years of age ([Table 3](#)). ieSET was associated with a significantly higher birth weight by >400 grams, whereas preterm births and perinatal mortality rates were less than half of those seen with iDET ([Table 4](#)). Patients in the ieSET group were more likely to experience a miscarriage (16% vs. 15%; AOR, 1.24; 95% CI, 1.16–1.32) within all age categories excluding women >40 years of age ([Table 3](#)), although this small difference may not be clinically significant.

Among women who achieved a live birth, an ieSET was associated with the need for more treatment cycles (1.7 ± 0.8 vs. 1.4 ± 0.6 ; AOR, 1.19; 95% CI, 1.16–1.21), a difference

that was consistent and statistically significant for all age categories other than women >40 years of age (Table 3). ieSET was also associated with a significantly longer time (mean difference of 32 days, 95% CI, 27–36) from treatment onset to the beginning of a pregnancy which resulted in delivery of a baby.

Lastly, we confirmed prior findings when considering only the result of the initial embryo transfer. Live birth rate was significantly less likely in the eSET group after adjustment for covariates in the full sample (AOR, 0.69; 95% CI, 0.66–0.72) and in both the fresh transfer (AOR, 0.71; 95% CI, 0.68–0.75) and frozen transfer (AOR, 0.64; 95% CI, 0.59–0.70) subsamples.

Patients in both the ieSET and iDET groups went on to have SET, eSET, DET, or multiple embryo transfer in up to 6 subsequent transfers. When evaluating all transfer cycles by patients in the ieSET group, 85% of transfers were eSET or subsequent SET, whereas in the iDET group, 95% of all transfers were DETs. When considering transfer cycles that resulted in pregnancy in each group, 83% of pregnancies in the ieSET group resulted from single embryo transfers (eSET or subsequent SET), and 97% of pregnancies in the iDET group resulted from DETs. In a sub analysis of patients in the ieSET group who went on to have eSET or DET for their second transfer, we did not find a statistically significant difference in CLBR when classifying the groups on the basis of their second transfer (63% vs. 66%; AOR, 0.94; 95% CI, 0.83–1.06). We did not conduct a sub analysis of outcomes for the iDET group on the basis of their second transfer as the proportion having eSET was low (301 patients with eSET vs. 3,427 patients with DET).

DISCUSSION

Multiple gestation pregnancies are a common complication of IVF treatment leading to high rates of prematurity and increased health care costs at delivery and adverse health outcomes for children. In the most recent national report from 2017, twinning rates from the initial IVF cycle in the United States ranged from 12.8% in women <35 years of age to 7.2% in women >42 years of age, numbers that, although improving in recent years, still compare unfavorably with the natural twinning rate of approximately 2% (1, 12). Although monozygotic twinning rates are increased with IVF compared with natural conceptions (13), most multiple gestations occur as a result of transferring >1 embryo in an IVF cycle. The practice of single embryo transfer is increasing in US IVF centers, but transfer of ≥ 2 embryos is still performed in 39% of initial embryo transfers in women <35 years of age and 51% of initial transfers in women aged 35–37 years (12). This is risky as almost half of all IVF-related multiple births occur from DET to patients with a good prognosis at <35 years of age or patients who are donor oocyte recipients (14). In addition, more than half of triplet and higher order multiples after ART result from monozygotic twinning after DET.

In our large national cohort of IVF cycles from 2014 to 2016, nearly twice as many patients had iDET compared to ieSET. When considering the reproductive potential of a cohort

of embryos (fresh and frozen) from 1 egg retrieval to achieve a live birth delivery, we found that the ieSET strategy was associated with a higher CLBR in all age groups, with statistical significance found for women <35 and 35–37 years of age. Furthermore, the multifetal delivery rate was much lower with ieSET compared with iDET, with statistical significance noted for all women ≤ 40 years of age. These advantages came at the expense of a longer time to ongoing pregnancy by approximately 32 days and the need for 0.3 more embryo transfer cycles on average. The ieSET was associated with significantly improved perinatal outcomes with a >400-gram increase in infant birth weight on average and preterm birth rates and perinatal mortality rates that were reduced by more than half of that seen in pregnancies conceived after iDET. The difference in time to pregnancy was not because of a difference in prematurity rates as our measure of time to pregnancy resulting in live birth did not include the length of the pregnancy. Differences in infant outcomes were likely due to the multiple fetal delivery rate, which is a known complication of DET.

We speculate the higher CLBR associated with ieSET results from cryopreserving the extra embryo that would have been transferred with iDET so that it is available for another transfer, if the initial transfer cycle does not produce an ongoing pregnancy. With embryo vitrification techniques, embryo survival after warming is >90% and studies suggest a similar CLBR in elective frozen embryo transfer compared with fresh embryo transfer (relative risk = 1.04; 95% CI, 0.97–1.11) (5). Perhaps having an additional embryo cryopreserved in the ieSET group improves the likelihood that an embryo transfer will occur eventually to a receptive endometrium.

We confirm prior studies showing that DET results in higher live birth rate in the initial transfer compared with eSET (7, 9). This suggests that patient selection is not playing a major role in our study findings. However, it is possible that there are inherent differences between the ieSET and iDET groups, and providers may direct those with better prognosis toward eSET. Despite controlling many variables, including the number of 2PN embryos and embryo quality, in our analysis, the iDET group had fewer total embryos either transferred or cryopreserved, which may have affected the outcomes.

A strength of our study was the use of the large prospective SART database that captured >90% of all IVF cycles performed in the United States. Cumulative IVF outcomes were determined through linkages between the initial cycle and subsequent cryopreserved embryo transfer cycles, allowing for the study of the reproductive potential of an IVF stimulation cycle. We acknowledge that this data does not represent the total reproductive potential from 1 retrieval as all embryos did not have to be transferred to be included in the data set. Further studies with much longer follow-up may be valuable for patient counseling.

We categorized the patients as having ieSET or iDET on the basis of the initial embryo transfer and if patients were not pregnant from the initial transfer, a variable number of embryos may have been transferred in later cryopreserved embryo transfer cycles, although most of the transfers were

SET in the ieSET group and DET in the iDET group. After ieSET, the cumulative live birth rates were similar between the second cycle eSET and DET, supporting the strategy of using SET for all cycles, particularly in patients with a good prognosis.

We chose not to include cycles in which the embryos had been biopsied and tested for aneuploidy (preimplantation genetic testing-A cycles) as the efficacy of this technique is unclear (15, 16). Further studies will be needed to assess the cumulative outcomes of eSET vs. DET within the patient population undergoing preimplantation genetic testing-A. We acknowledge that the data are necessarily several years delayed to ensure the complete reporting of pregnancy outcomes for the entire follow-up period. The most recent finalized 2017 data and preliminary 2018 data from SART show a gratifying increase in eSET utilization resulting in a lower multiple birth rate than was seen in our dataset.

A weakness of this study is that there were many differences in patient and cycle characteristics between the ieSET and iDET groups. Table 1 demonstrates these differences, particularly the number of 2PN embryos and good quality embryos to transfer. These statistically significant differences are in part due to the large sample size and some of these differences may not be clinically significant. Of note, there was a high average antimüllerian hormone level in both groups, which may be related to the higher percentage of women ≤ 37 years of age in the cohort, 94% of women in the eSET group, and 80% of women in the DET group. We attempted to control for the many observed differences through robust statistical methods. However, we acknowledge that, in a retrospective cohort study, there may be other population differences not captured in the database that may be significant confounders influencing the outcomes of our study.

It is possible that there are clinic-based factors that drive eSET vs. DET transfer such as overall live birth rates at clinics. We did not have access to clinic-specific data in the SART dataset to assess this possibility.

Despite the advantages of eSET, DET still is practiced commonly in US IVF centers. There is both economic and patient pressure to achieve a pregnancy quickly with fewer embryo transfers. In a retrospective cohort study analyzing a claims database, the adjusted total all-cause health care cost was 5 times as much in delivery of twins compared with singleton deliveries (17). Given these differences, a multiple pregnancy may contribute \$104,831 (95% CI, \$103,402–106,280) to overall health care costs beyond the cost of an additional transfer cycle. Despite the economic advantages of eSET for the health care system, gaps in insurance coverage for fertility treatment often place the financial burden of additional transfer cycles on patients. In addition to financial concerns, patients frequently cite concerns related to the burden of time and emotional toll of fertility treatment as important factors in their decision to both undergo an initial IVF cycle and to return for care (18). Although all of these concerns may limit the patients' willingness to pursue eSET, our IVF center has found that simple education materials improve the knowledge of twin pregnancy risks and affect patient decision making (19). Mandatory single blastocyst transfer policies for patients with a good prognosis can be

another successful tool for clinics to reduce multiple rates through the reduction of DET rates. By educating patients on the benefits of ieSET early in their care, including improved CLBR, opportunity for more transfers, and decreased risk of pregnancy and delivery complications, patients and providers can make a shared educated decision on the number of embryos to transfer.

The CDC and SART have engaged in a campaign to encourage "Having healthy infants, one at a time" to curb the iatrogenic multiple birth epidemic from IVF. As part of that initiative, in 2017 the practice committee of SART and the American Society for Reproductive Medicine issued an opinion that only 1 embryo be transferred to women <38 years of age who had a favorable prognosis based, in part, on the presence of an extra good quality embryo for cryopreservation. Our findings should be reassuring to the patients and physicians following these guidelines that the CLBR will certainly not be negatively impacted and will likely be improved. Without question, eSET will result in improved perinatal and neonatal outcomes. Despite the additional time to pregnancy and need for more embryo transfer cycles, a strategy of ieSET is likely to be cost-effective, given the relatively low costs of an embryo transfer cycle compared with the high medical costs associated with multiple gestation pregnancies and premature infants. Our study findings of improved CLBR and perinatal outcomes can be used as additional arguments for the insurance industry to incentivize ieSET and pay for additional frozen embryo transfer cycles to improve the cost-effectiveness of IVF.

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