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Costs of achieving live birth from assisted reproductive technology: a comparison of sequential single and double embryo transfer approaches

Sara Crawford, Ph.D., **Sheree L. Boulet, Dr.P.H., M.P.H.**, **Allison S. Mneimneh, M.P.H.**, **Kiran M. Perkins, M.D., M.P.H.**, **Denise J. Jamieson, M.D., M.P.H.**, **Yujia Zhang, Ph.D.**, and **Dmitry M. Kissin, M.D., M.P.H.**

Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

Abstract

Objective—To assess treatment and pregnancy/infant-associated medical costs and birth outcomes for assisted reproductive technology (ART) cycles in a subset of patients using elective double embryo (ET) and to project the difference in costs and outcomes had the cycles instead been sequential single ETs (fresh followed by frozen if the fresh ET did not result in live birth).

Design—Retrospective cohort study using 2012 and 2013 data from the National ART Surveillance System.

Setting—Infertility treatment centers.

Patient(s)—Fresh, autologous double ETs performed in 2012 among ART patients younger than 35 years of age with no prior ART use who cryopreserved at least one embryo.

Intervention(s)—Sequential single and double ETs.

Main Outcome Measure(s)—Actual live birth rates and estimated ART treatment and pregnancy/infant-associated medical costs for double ET cycles started in 2012 and projected ART treatment and pregnancy/infant-associated medical costs if the double ET cycles had been performed as sequential single ETs.

Result(s)—The estimated total ART treatment and pregnancy/infant-associated medical costs were $580.9 million for 10,001 double ETs started in 2012. If performed as sequential single ETs, estimated costs would have decreased by $195.0 million to $386.0 million, and live birth rates would have increased from 57.7%–68.0%.

Conclusion(s)—Sequential single ETs, when clinically appropriate, can reduce total ART treatment and pregnancy/infant-associated medical costs by reducing multiple births without lowering live birth rates.

Reprint requests: Sara Crawford, Ph.D., 4770 Buford Highway NE, MS F-74, Atlanta, Georgia 30341 (sgv0@cdc.gov).

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Keywords

Sequential single embryo transfer (SET); double embryo transfer (DET); assisted reproductive technology (ART); in vitro fertilization (IVF); infertility

The introduction of assisted reproductive technology (ART) has led to an increase in multiple births in the United States (1). Multiple births pose health risks for mother and child. For mothers, risks include gestational diabetes, pregnancy-induced hypertension, cesarean delivery, and hemorrhage, whereas for infants, risks include preterm birth, low birth weight, birth defects, cerebral palsy, autism, and death (2–8). The best way to avoid multiple births after ART treatment is to reduce the number of embryos transferred during an ART cycle. For patients who are considered to have a good prognosis (good prognosis patients), the use of elective single embryo transfer (ET) (eSET) minimizes the risk of multiple births (9, 10). Although reducing the number of embryos transferred in fresh cycles would reduce multiple births, it would also likely reduce live birth rates. However, performing sequential single ET (SET) could reduce multiple births yet preserving live birth rates. Sequential SET involves performing a fresh eSET cycle and cryopreserving extra embryos for later use, and then performing a frozen SET cycle if the fresh eSET cycle does not result in a live birth.

The use of sequential SET instead of double ET (DET) also would affect the costs associated with ART treatment and any resulting pregnancies, births, and infants born. Because the number of cycles required to achieve pregnancy and live birth would likely increase, on average, we theoretically would expect an increase in total ART treatment costs. However, the expected reduction in multiple births also would likely reduce total pregnancy/infant-associated medical costs (prenatal, delivery, and postpartum) (11). Given that the pregnancy/infant-associated medical costs per delivery are typically higher than ART treatment costs per cycle, particularly for multiple births, we might expect a net reduction in total costs.

The objectives of this study were to assess ART treatment and pregnancy/infant-associated medical costs and birth outcomes for cycles among a subset of ART patients using elective DET and to project the difference in costs and outcomes had the cycles instead been sequential SETs.

MATERIALS AND METHODS

Data Source

We used data from the Centers for Disease Control and Prevention’s National ART Surveillance System, which contains ART cycle characteristics, patient characteristics, and treatment and pregnancy outcomes for >97% of all ART cycles performed in the United States (12). Our analysis included all fresh, autologous eSETs or elective DETs performed in 2012 among patients who were good candidates for eSET, defined as those younger than 35 years of age with no previous ART treatment (13). Because the number of embryos available for transfer is not collected in the National ART Surveillance System, we classified a transfer as elective if at least one embryo was cryopreserved. For fresh autologous transfers among patients younger than 35 years of age with no previous ART cycles who

used eSET but did not achieve a live birth, we also analyzed the first frozen SET occurring after the failed first fresh eSET. The frozen cycle had to occur within 1 year of the fresh cycle. Undergoing a fresh eSET and then a frozen SET, if needed, is hereafter referred to as "sequential SET."

Characteristics

Patient and cycle characteristics were compared between fresh eSET and fresh elective DET cycles. Patient characteristics included demographics, pregnancy history, and infertility diagnosis. Cycle characteristics included the number of oocytes retrieved, embryo manipulation techniques used, day of ET, and cryopreservation. The χ^2 tests, with an adjustment for clustering of cycles by ART clinic, were conducted to determine statistically significant differences in characteristics between the two groups.

Costs

Chambers et al. (14) reported the cost of a fresh transfer cycle to be $12,513 and the cost of a frozen cycle to be $3,035 in 2006 US dollars. We assumed average ART treatment costs to be $15,715 per fresh cycle and $3,812 per frozen cycle after converting costs to 2012 US dollars and adjusting costs according to the Consumer Price Index for All Urban Consumers for Medical care services (15). The ART treatment costs include all costs before achieving pregnancy, such as stimulation, retrieval, embryology, transfer, and cryopreservation. Lemos et al. (11) reported average pregnancy/infant-associated medical costs for an ART birth to be $26,922 per singleton, $115,238 per twin, and $434,668 per triplet or higher-order live birth in 2010 US dollars. We assumed average pregnancy/infant-associated medical costs to be $28,829 per singleton, $123,402 per twin, and $465,464 per triplet or higher-order live birth after converting costs to 2012 US dollars and adjusting costs according to the Consumer Price Index for All Urban Consumers for Medical care services (15). Medical cost estimates include all payments made by private insurers or patients for maternal costs from 27 weeks before delivery to 1 month after delivery and for infant costs through the first year of life among commercially insured women 19–45 years of age.

Estimated Costs and Live Birth Rates, DET

We estimated total ART treatment and pregnancy/infant-associated medical costs for the 10,001 DET cycles started in 2012 by multiplying the number of ART transfers and births by average treatment and medical costs. We calculated live birth rates as the number of live births per number of fresh DET, multiplied by 100. We estimated the number of live-born infants by assuming that no infants were stillborn in a multiple birth, rather than reporting the actual number of live-born infants for these cycles, for comparability with projected numbers.

Projected Costs and Live Birth Rates, DET Performed as Sequential SET

We projected ART treatment and pregnancy/infant-associated medical costs for the DET cycles started in 2012 by assuming that they had been performed as sequential SET cycles. We calculated live birth rates for the actual number of sequential SET cycles started in 2012 and used these rates to project the number of transfers and births. We multiplied the

projected number of transfers and births by the average treatment and medical costs to estimate total ART treatment and pregnancy/infant-associated medical costs. We calculated live birth rates as the number of live births per number of fresh eSET, multiplied by 100. We estimated the number of live-born infants by assuming that no infants were stillborn in a multiple birth.

We conducted a subanalysis to make the sequential SET and DET groups more comparable. All analyses were repeated among patients who had at least 15 oocytes retrieved, did a blastocyst transfer, and cryopreserved at least three embryos.

For the number of live births among cycles started in 2012, we suppressed any numbers 1–4 to protect patient confidentiality, reporting instead the possible range $1 \leq n \leq 4$. We also suppressed any numbers that would allow the suppressed number to be calculated. We used an average live birth rate for these suppressed numbers by taking the average of all possible live birth rates for all possible values of n. This study was approved by the Center for Disease Control and Prevention's Institutional Review Board.

RESULTS

Characteristics

A total of 14,398 fresh ART cycles resulting in ET among patients younger than 35 years of age with no prior ART cycles and cryopreservation of at least one embryo were started in 2012. Among these cycles, 4,129 (28.7%) were eSET and 10,001 (69.5%) were elective DET. Patient and cycle characteristics of eSET and DET groups differed significantly with regard to ART diagnosis and cycle characteristics, although the magnitude of most differences was relatively small (Table 1). Compared with the DET group, the eSET group had a lower percentage of transfers among patients with diminished ovarian reserve (4.3% vs. 6.4%), endometriosis (8.8% vs. 12.2%), tubal factor infertility (13.9% vs. 16.0%), and male factor infertility (38.4% vs. 41.8%), but a higher percentage among patients with some other (11.8% vs. 9.0%) or unexplained (17.8% vs. 14.5%) reason for ART. The eSET group had a higher percentage of retrievals of 20 or more oocytes (36.1% vs. 29.4%) and a higher percentage of transfers using preimplantation genetic diagnosis (5.9% vs. 3.3%) than the DET group, but a lower percentage of transfers using assisted hatching (13.1% vs. 23.9%) or intracytoplasmic sperm injection (ICSI) (68.9% vs. 78.0%). The eSET group had a larger percentage of blastocyst transfers (90.1% vs. 68.6%) than the DET group and a larger percentage of transfers cryopreserving six or more embryos (32.3% vs. 23.2%).

Costs and Live Birth Rates, DET

The 10,001 DET cycles performed in 2012 yielded total estimated ART treatment costs of $157.2 million (Fig. 1). These cycles resulted in 3,300 (33.0%) singleton, 2,399 (24.0%) twin, and 70 (0.7%) triplet or higher-order live births, with estimated total pregnancy/infant-associated medical costs of $423.8 million. Total estimated costs were $580.9 million, or $58,087 per fresh cycle.

The 10,001 DET cycles performed in 2012 resulted in a live birth rate of 57.7% and a multiple live birth rate of 24.7%. The estimated total number of live born infants was 8,308.

Costs and live Birth Rates, DET Performed as Sequential SET

Live birth rates for sequential SET cycles started in 2012 were calculated to project costs and birth outcomes for the DET cycles if they had been performed instead as sequential SETs (Fig. 2). Of the 4,129 fresh, autologous eSET cycles started in 2012, 49.2% resulted in singleton live births, approximately 1.0% in twin live births, and approximately 0.1% in triplet or higher-order live births. Of those that did not achieve a live birth, 698 (34.0%) attempted a frozen SET. For the frozen cycles, 35.2% resulted in a singleton live birth, approximately 0.4% resulted in a twin live birth, and none resulted in a triplet or higher-order live birth.

If the 10,001 DET cycles performed in 2012 had instead been performed as sequential SET, the estimated ART treatment costs for the fresh eSET would have been identical to the ART treatment costs for DET, at $157.2 million (Fig. 3). However, because 49.8% of eSET cycles in 2012 did not result in a live birth, we would expect 4,978 additional frozen ETs. The frozen cycles would have cost an additional $19.0 million, for total projected ART treatment costs of $176.1 million.

Given the success rates seen for sequential SET in Figure 2, we would expect 49.2% of the 10,001 fresh eSET cycles to result in singleton live births (n = 4,922), 1.0% in twin live births (n = 96), 0.1% in triplet or higher-order live births (n = 7), and 49.8% (n = 4,978) to not have resulted in a live birth. Assuming that all 4,978 patients without a live birth would undergo an additional frozen SET, we would expect 35.2% to result in singleton live births (n = 1,755), 0.4% in twin live births (n = 18), and no triplet or higher-order live births. The total projected pregnancy/infant-associated medical costs for births resulting from sequential SET would have been $209.8 million.

If the 10,001 DET cycles performed in 2012 had been performed as sequential SET, the total estimated ART treatment and pregnancy/infant-associated medical costs would have been $386.0 million rather than the $580.9 million estimated for DET, yielding an estimated savings of $195.0 million, or a 34% reduction in costs. The average total cost per fresh cycle would have been approximately $38,600, as compared with $58,100 for DET.

The hypothetical 10,001 sequential SET cycles would have resulted in an estimated 6,798 live births, of which 121 would have been multiple live births, for a projected cumulative live birth rate of 68.0% and a projected cumulative multiple live birth rate of 1.2%. The estimated total number of infants born would have been 6,926.

Subanalysis

When we restricted our analysis to blastocyst transfers among patients who retrieved at least 15 oocytes and cryopreserved at least three embryos, results were similar (data not shown). For 3,117 DET cycles performed in 2012, the live birth rate was 60.8%, the multiple live birth rate was 29.1%, and the total estimated ART treatment and pregnancy/infant-associated medical costs were $199.8 million, or $64,093 per fresh cycle. Had the cycles been performed as sequential SET, the estimated live birth rate would have been 70.4%, the estimated multiple live birth rate 1.6%, and the estimated total costs $122.6 million, or $39,342 per fresh cycle.

DISCUSSION

Although sequential SET among women younger than 35 years of age who are undergoing their first ART cycle results in higher treatment costs compared with DET ($176.1 million vs. $157.2 million), estimates from this analysis show pregnancy/infant-associated medical costs to be markedly lower ($209.8 million vs. $423.8 million), resulting in lower overall costs ($386.0 million vs. $580.9 million). These cost savings are achieved while increasing overall live birth rates (57.7% for DET and 68.0% for sequential SET) due to a reduction in multiple birth rates (24.7% for DET and 1.2% for sequential SET). For this population of women, sequential SET rather than DET would result in lower total costs, for a potential savings of $195.0 million in 2012.

The 10,001 DET cycles included in the present study represent only 12.4% of all fresh autologous transfers performed in 2012; however, the projected decrease of 2,348 multiple births accounts for 29.3% of multiple births resulting from all fresh autologous transfers performed in 2012. The multiple birth rate for all 80,783 fresh autologous transfers performed in 2012 was 9.9%. If 10,001 of these transfers had been performed as sequential SET, the multiple birth rate would have been only 7.0% (12).

These results align with other studies that have found cumulative live birth rates for two SETs to be at least as high as live birth rates for one DET (16–18) and two SETs to be more cost effective than one DET (19–21). These studies were small in size compared with our study or did not explore both birth rates and costs.

The present study shows an opportunity for cost savings among patients younger than 35 years of age who are having their first ART cycle with additional embryos available for transfer if SETs rather than DETs are performed. These cost savings could be even higher if patients meeting less stringent criteria—such as good prognosis patients 35–37 years of age—are considered for sequential SET (9, 22). A barrier to realizing this potential savings is that ART treatment costs in the United States are typically paid by the patient, whereas most pregnancy/infant-associated medical costs are typically paid by an insurer. Currently, only eight states mandate insurance coverage for ART procedures, and coverage in these states varies widely (23). The potential for increased ART treatment costs may dissuade ART patients from selecting sequential SET instead of DET.

Had insurance covered ART treatment costs in addition to pregnancy/infant-associated medical costs in 2012—and required sequential SET as a condition for coverage—our estimates suggest a $37.8 million savings versus what was actually spent on just pregnancy/infant-associated medical costs for DET cycles performed in 2012, despite the increased cost for ART treatment. Although these numbers indicate a savings with insurance coverage of ART treatment when a limited number of embryos are transferred, our analysis does not take into account the additional cost of providing ART treatment to patients who do not meet the good prognosis criteria or the additional treatment and medical costs that would arise from an increase in ART use as a result of ART treatment coverage (24–26). It also assumes that insurance is paying all of the pregnancy/infant-associated medical costs, when a portion of these costs are likely paid by the patient. An alternative mechanism for encouraging

sequential SET would be incentives offered by the ART treatment provider, such as a discounted rate on additional frozen cycles, if needed after a fresh eSET, or package pricing for sequential SET cycles.

This study has several limitations. First, when calculating projected costs for DET performed as sequential SET, we assumed that the DET group would experience the same success rates as the sequential SET group. Differences in characteristics between the eSET and DET groups could result in the DET group experiencing lower success rates if attempting eSET instead. However, a subanalysis of cycles that were more similar between the eSET and DET groups in some of these characteristics did not affect results. Second, this study does not take into account the increased potential for patient dropout when performing two cycles instead of one. Third, this study does not take into account the reduction in total infants born and the additional ART treatment and pregnancy/infant-associated medical costs that would be incurred for patients who want additional children but birthed fewer infants as a result of choosing sequential SET. Fourth, the medical cost estimates include only direct medical costs through the first year of life, not nonmedical costs (e.g., educational intervention programs) or costs beyond the first year. Finally, these cost estimates do not take into account that singletons born after DET generally have lower birth weights and earlier gestational ages than singletons born after eSET (27, 28), thus requiring more medical intervention. As a result, these estimates may underestimate the cost savings.

This study demonstrates that the use of sequential SET rather than DET during ART can produce overall cost savings. More important, this approach can improve perinatal outcomes among children conceived through ART and reduce morbidity among their mothers by reducing multiple births and their sequelae. However, the mechanism for transitioning patients from DET to sequential SET is unclear because patients are typically responsible for paying ART treatment costs in the United States. Other countries, such as Canada and Belgium, have provided public funding for ART treatments in exchange for a SET requirement in good prognosis patients (26, 29, 30).

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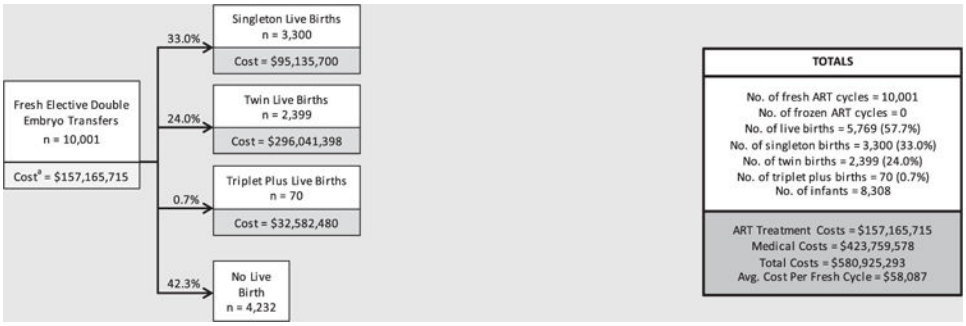

FIGURE 1.

Estimated assisted reproductive technology (ART) treatment and pregnancy/infant-associated medical costs for 10,001 fresh autologous elective double ETs started in 2012. The ART treatment costs are estimated to be $15,715 per fresh cycle and $3,812 per frozen cycle (14). Medical costs are estimated to be $28,829, $123,402, and $465,464 per singleton, twin, and triplet plus ART live birth, respectively (11). Medical costs include maternal costs from 27 weeks before delivery to 1 month after delivery and infant costs through the first year of life. Predicted number of births and transfers are always rounded up to the next whole number. For comparability, the number of infants is approximated as the number of singleton live births + 2*(number of twin live births) + 3*(number of triplet or higher-order live births). ART = assisted reproductive technology; Avg = average.

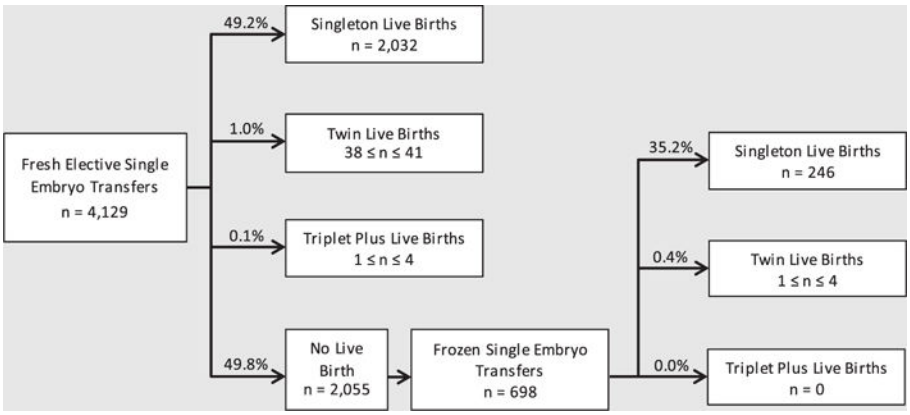

FIGURE 2.

Live birth rates for 4,129 fresh autologous elective single ETs started in 2012 and subsequent frozen single ETs. The number of triplet plus live births after fresh elective single ETs is 1–4 and the number of twin live births is 38–41. The number of twin live births after frozen single ETs is 1–4. The true numbers are suppressed to protect confidentiality, either because the value is small or because knowledge of the value would allow for the calculation of a small value. True success rates for twin and triplet plus live births after fresh elective single ETs and twin live births after frozen single ETs are suppressed to prevent calculation of the number of live births. We used the average success rate across all possible values for n as an approximation.

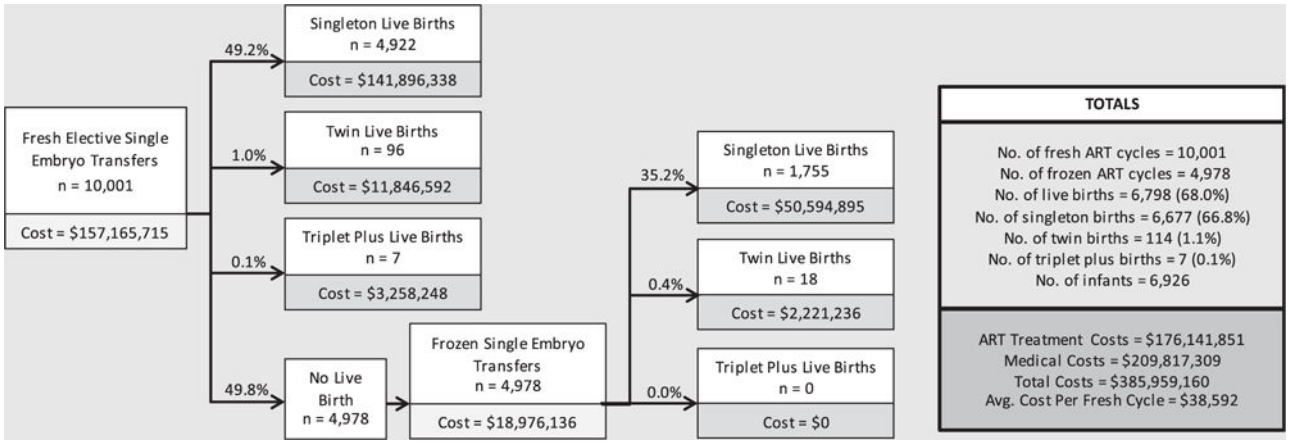

FIGURE 3.

Projected assisted reproductive technology (ART) treatment and pregnancy/infant-associated medical costs for 10,001 autologous cycles if performed as sequential elective single ETs. Live birth rates for 4,129 fresh elective single ET cycles performed in 2012 (Fig. 2) are applied to the 10,001 cycles originally performed as elective double ET cycles in 2012. The ART treatment costs are estimated as $15,715 per fresh cycle and $3,812 per frozen cycle (14). Medical costs are estimated as $28,829, $123,402, and $465,464 per singleton, twin, and triplet plus ART live birth, respectively (11). Medical costs include maternal costs from 27 weeks before delivery to 1 month after delivery and infant costs through the first year of life. The predicted number of births and transfers are always rounded up to the next whole number. For comparability, the number of infants is approximated as the number of singleton live births + 2*(number of twin live births) + 3*(number of triplet or higher-order live births). ART = assisted reproductive technology; Avg = average.

TABLE 1

Characteristics of fresh elective single ETs (eSET) and fresh elective double ETs (DET) among patients younger than 35 years of age with no prior ART cycles who cryopreserved at least one embryo in 2012.

	eSET (n = 4,129)		DET (n = 10,001)		
Characteristic	**N**	**%**	**N**	**%**	***P* value**
Age (y)					.63
≤30	1,872	45.3	4,602	46.0	
31–32	1,168	28.3	2,743	27.4	
33–34	1,089	26.4	2,656	26.6	
Gravidity					.39
0	2,657	64.5	6,363	63.8	
1	839	20.4	1,990	20.0	
≥2	623	15.1	1,618	16.2	
Parity					.07
0	3,394	82.5	8,406	84.4	
1	546	13.3	1,123	11.3	
≥2	174	4.2	430	4.3	
Race[a]					<.001
Non-Hispanic white	2,110	73.1	5,007	73.0	
Non-Hispanic black	160	5.5	452	6.6	
Asian/Pacific Islander	429	14.9	730	10.6	
Hispanic	182	6.3	661	9.6	
Other	5	0.2	14	0.2	
Body mass index (BMI)[a]					<.001
<18.5	133	3.8	252	3.1	
18.5–24.9	2,030	58.6	4,450	55.0	
25–29.9	800	23.1	1,951	24.1	
≥30	500	14.4	1,442	17.8	
ART diagnoses (not mutually exclusive)					
Female factor infertility					
Diminished ovarian reserve	178	4.3	641	6.4	<.001

	eSET (n = 4,129)		DET (n = 10,001)		
Characteristic	**N**	**%**	**N**	**%**	***P* value**
Endometriosis	365	8.8	1,217	12.2	<.001
Ovulation disorders	986	23.9	2,264	22.6	.16
Tubal factor	574	13.9	1,596	16.0	.02
Uterine factor	178	4.3	362	3.6	.11
Male factor infertility	1,586	38.4	4,183	41.8	.006
Other reason for infertility	487	11.8	898	9.0	<.001
Unexplained infertility	734	17.8	1,449	14.5	<.001
No. of oocytes retrieved					<.001
2–4	43	1.0	81	0.8	
5–9	486	11.8	1,472	14.7	
10–14	1,007	24.4	2,882	28.8	
15–19	1,102	26.7	2,629	26.3	
≥20	1,491	36.1	2,937	29.4	
Assisted hatching	539	13.1	2,391	23.9	<.001
Intracytoplasmic sperm injection	2,843	68.9	7,797	78.0	<.001
Preimplantation genetic diagnosis	245	5.9	326	3.3	<.001
Embryo stage[b]					<.001
Cleavage (day 2–3)	371	9.0	2,927	29.3	
Blastocyst (day 5–6)	3,721	90.1	6,862	68.6	
No. of embryos cryopreserved					<.001
1–2	1,141	27.6	4,045	40.5	
3–5	1,654	40.1	3,640	36.4	
≥6	1,334	32.3	2,316	23.2	

Note: ART = assisted reproductive technology.

[a]Race data were missing for 30% of the eSET group and 31% of the DET group. BMI data were missing for 16% of the eSET group and 19% of the DET group. Percentages and *P* values were calculated for the data available.

[b]A small percentage of transfers occurred on days 1 and 4. Data not shown.