Adherence to embryo transfer guidelines in favorable-prognosis patients aged less than 35 years using autologous oocytes and in recipients using donor oocytes: a Society for Assisted Reproductive Technology Clinic Outcome Reporting System study

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Objective: To measure the consequences of nonadherence with the 2013 American Society for Reproductive Medicine elective single embryo transfer (eSET) guidelines for favorable-prognosis patients.
Design: Retrospective cohort.
Setting: In vitro fertilization clinics.
Patient(s): A total of 28,311 fresh autologous, 2,500 frozen-thawed autologous, and 3,534 fresh oocyte-donor in vitro fertilization cycles in 2014–2016 at Society for Assisted Reproductive Technology-reporting centers.
Intervention(s): Patients aged <35 years or using donors aged <35 years underwent first blastocyst transfer.
Main Outcome Measure(s): Singleton birth rate, gestational age at delivery, and birth weight were compared between the eSET and non-eSET groups using the chi-square or Fisher's exact test or t-tests.
Result(s): Among fresh transfers, 15,643 (55%) underwent eSET. Live births after non-eSETs were less likely singletons (38.0% vs. 96.5%; adjusted relative risk [aRR], 0.56) and more likely complicated by preterm delivery (55.0% vs. 20.1%; aRR, 2.39) and low birth weight (<2,500 g) (40.1% vs. 10.6%; aRR, 3.4) compared with those after eSET.

Among frozen-thawed transfers, 1,439 (58%) underwent eSET. Live births after non-eSETs were less likely singletons (41.9% vs. 95.2%; aRR, 0.69; 95% confidence interval, 0.66–0.73) and more likely complicated by preterm delivery (56.4% vs. 19.5%; aRR, 2.6; 95% confidence interval, 2.2–3.1) and low birth weight (38.0% vs. 8.9%; aRR, 3.9) compared with those after eSET.

Among fresh donor oocyte transfers, 1,946 (55%) underwent eSET. Live births after non-eSETs were less likely singletons (31.3% vs. 97.3%; aRR, 0.48) and more likely complicated by preterm delivery (61.1% vs. 25.7%; aRR, 2.09) and low birth weight (44.3% vs. 11.7%; aRR, 3.39) compared with those after eSET.

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Conclusion(s): Nonadherence with transfer guidelines was associated with dramatically increased multiple pregnancies, preterm births, and low birth weights. (Fertil Steril® 2022;117:548-59. ©2021 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Embryo transfer, guidelines, multiple pregnancy, blastocyst, elective single embryo transfer

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Women who conceive through assisted reproductive technologies (ARTs), including in vitro fertilization (IVF), are more likely to experience a multiple pregnancy than women who conceive naturally, primarily because of the transfer of multiple embryos (1). Infants born from multiple pregnancies are more likely to experience obstetric and neonatal complications, including preterm delivery and low birth weight (1). For these reasons, the American Society for Reproductive Medicine (ASRM) Practice Committee endorses that the objective of infertility treatment is to "maximize the probability of pregnancy while minimizing the risk of a multiple gestation" (2).

While specific interventions for reducing the risk of multiple gestations vary on the basis of the planned treatment and patient characteristics, the ASRM together with its affiliate society, the Society for Assisted Reproductive Technology (SART), has issued practice guidelines since 1998 limiting the maximum number of embryos to transfer for IVF. As the IVF success rates continued to improve, increasingly strict guidelines were issued during guideline updates in 1999, 2004, 2006, 2008, 2009, 2013, and 2017 to reduce the probability of multiple gestations (3, 4).

Since 2006, the ASRM and SART practice guidelines have recommended that patients aged <35 years with a favorable prognosis, defined as the first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle, receive no more than 1 blastocyst (5). This recommendation has been reaffirmed in the most recent 2017 guidelines and extended to several other patient categories, including women aged <38 years and women of all ages receiving euploid embryos (3). However, a SART national cohort study identified that a single embryo was transferred in only 29% of fresh first autologous transfers of blastocyst-stage embryos in women aged <35 years performed in 2011–2012 (6).

We hypothesized that compliance with the guidelines in the most recently available 2014–2016 data has improved since 2012 but that several patients still underwent transfers in excess of the limits. Moreover, we hypothesized that the obstetric complications in these most favorable-prognosis patients would remain higher among patients who undergo transfer of >1 embryo than those who undergo elective single embryo transfer (eSET). In this study, to best estimate noncompliance with the guidelines across clinics in the United States, we restricted the cohort to the most favorable-prognosis patients with the potential for eSET of blastocysts after excluding for all identifiable justifications for transfer of >1 embryo.

MATERIALS AND METHODS

The data used for this study were obtained from the SART Clinic Outcome Reporting System (SART CORS). Data were collected from participating clinics through voluntary submission, verified by the SART, and reported to the Centers for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The SART maintains the Health Insurance Portability and Accountability Act-compliant business associate agreements with reporting clinics. In 2004, after a contract change with the CDC, the SART gained access to the SART CORS data system for the purposes of conducting research. In 2017, 82% of all ART clinics in the United States were SART members (7). Participating clinics are expected to prospectively report cycles, although retrospective reporting is accepted. This so-called "retrieval cycle start report rate" is prominently displayed on the summary report on the SART website for each clinic to discourage selective reporting, although the national prospective report rate is not available. Prospective reporting is defined as reporting to the SART within 4 days of the start of gonadotropins for oocyte retrieval/IVF cycles, within 4 days of recipient medication start for oocyte donation cycles, and before embryo thaw for frozen-thawed embryo transfers (FETs).

The data in the SART CORS are validated annually with 7%–10% of clinics receiving on-site visits for chart review on the basis of an algorithm for clinic selection. During each visit, data reported by the clinic are compared with information recorded in patients' charts. In 2019, records for 2014 cycles at 34 clinics were randomly selected for full validation, along with 213 fertility preservation cycles selected for partial validation. The full validation included a review of 1,300 cycles for which a pregnancy was reported. Nine of 11 data fields selected for validation were found to have discrepancy rates of ≤5% (7). The exceptions were the diagnosis field, which, depending on the diagnosis, had a discrepancy rate between 2.5% and 17.8%, and the start date, which had an 8.4% discrepancy rate (7). Obstetric outcomes in the SART CORS including live birth/fetal death, plurality, birth date, and singleton birth weight were validated in a study comparing 9,092 ART deliveries in Massachusetts in 2004–2008 with state vital records of live birth and fetal death certificates. SART-reported outcomes from the Massachusetts ART records were validated to have >95% agreement with vital records (8).

To measure adherence to guidelines for favorable-prognosis patients undergoing blastocyst transfer, we searched the SART CORS retrospective cohort for IVF cycles

performed in patients with oocyte age (donor or autologous) of <35 years from 2014 to 2016. The 2013 guidelines for favorable prognosis were used, namely, first cycle of IVF, good embryo quality, excess embryos available for cryopreservation, or previous successful IVF cycle.

Rather than identifying patients who were considered to have a favorable prognosis by any 1 of the 4 criteria (transfer limit recommendations apply to patients meeting just 1 criterion), we required that patients met all of the first 3 criteria, namely, first cycle of IVF, good embryo quality, and excess embryos available for cryopreservation (a previous successful IVF cycle is incompatible with undergoing a first cycle).

However, to aid in comparison with the published results of Keyhan et al. (6), a secondary cohort of autologous fresh IVF cycles was also defined using this prior study's criteria, defined as the first cycle in women aged <35 years undergoing blastocyst transfers. Good embryo quality or excess embryos were not required.

The first cycle of IVF implied the first embryo transfer (other than prior autologous cycles if undergoing a donor cycle) with an embryo from the first cycle of IVF. Good embryo quality in the SART grading system corresponded to a blastocyst with grade 3BB or better by the Gardner–Schoolcraft morphology (9), an alphanumeric system scoring expansion (scales 1–5), inner cell mass (scales A–C), and trophectoderm (scales A–C). Excess embryo availability was defined and analyzed separately for the fresh autologous, frozen-thawed autologous, and fresh donor cycle cohorts.

An autologous fresh cycle meeting criteria for excess embryos generated at least 2 usable blastocysts, and the highest-quality embryo among the embryos transferred fresh was 3BB or better. The second blastocyst must have been either cryopreserved or transferred fresh.

An autologous FET cycle meeting criteria for excess embryos followed a stimulation cycle in which at least 2 blastocysts were cryopreserved and none were transferred fresh. Moreover, the highest-quality blastocyst among the embryos transferred in the FET was graded 3BB or better at the time of cryopreservation.

A fresh donor oocyte cycle meeting criteria entailed a fresh transfer of a fertilized donor oocyte into a patient with a synchronized prepared endometrium. Embryo(s) must have originated from donors aged <35 years, with at least 2 blastocysts generated, including 1 grade 3BB or better transferred into the recipient and a second embryo of any quality either transferred or cryopreserved.

Autologous or donor oocyte cycles entailing transfer into patients with an infertility etiology of recurrent pregnancy loss were excluded. Frozen cycles using preimplantation genetic testing (PGT) for some or all of the embryos were excluded. Oocyte cryopreservation and gamete intrafallopian transfer cycles were excluded. Any patient with a prior reported history of autologous embryo transfer, fresh or frozen-thawed, in the SART CORS database was excluded for autologous analyses.

The measured variables included patient age at the start of cycle, donor age at IVF cycle stimulation (donor cycles only), infertility etiology, body mass index (BMI), maximum follicle-stimulating hormone (FSH) (on cycle day 2, 3, or 4, or on day 10 of a clomiphene challenge test), anti-Müllerian hormone (AMH) in the year before IVF, parity, number of oocytes retrieved, number of embryos cryopreserved, and blastocyst grade at the time of cryopreservation. Regarding infertility etiology, diminished ovarian reserve was defined as a high FSH or estradiol level in the early follicular phase or during a clomiphene challenge test or reduced ovarian volume because of congenital, medical, surgical, or other causes. The SART CORS database does not specify the cutoff levels for "high" FSH, "high" estradiol, or "reduced" ovarian volume.

The primary outcome was adherence with the contemporaneous 2013 ASRM embryo transfer guidelines. The secondary outcomes included the clinical pregnancy rate, live birth rate, singleton rate among live births, gestational age at delivery, and birth weight. Clinical pregnancy was defined as sonographic visualization of an intrauterine gestational sac. Live birth was defined as delivery of a live-born infant at $\geq$24 weeks' gestation. Complete data were available for all primary and secondary outcomes.

Cycles were stratified into adherent (1 embryo transferred) and nonadherent ($\geq$2 embryos transferred) subsets. Summary statistics were computed as mean $\pm$ standard deviation along with median and interquartile range for continuous data and number and percent for categorical data. Summary statistics were computed after removal of missing demographic data. *P* values were generated on the basis of the chi-square or Fisher exact tests or t-tests, as appropriate.

In the primary analyses, unadjusted absolute differences in birth outcomes between the eSET groups were presented along with 95% confidence intervals (CIs). In the secondary analyses, adjusted absolute differences were estimated using multivariable binomial regression models (for binary outcomes) and linear regression models (for continuous outcomes such as birth weight and gestational age), adjusting for a set of prespecified assumed confounders: patient age at cycle start, number of oocytes retrieved, donor age at start (donor transfers only), BMI, etiology, maximum FSH, and AMH (autologous transfers only). Additionally, the model-based estimates of the relative risk for binomial outcomes were generated and presented along with 95% CIs and *P* values. For all models of birth weight outcomes, data were analyzed at the birth level; therefore, generalized estimating equation-based estimates using an exchangeable correlation structure were used to account for correlation between birth weights from a nonsingleton pregnancy. In the case of nonconvergence of any full binomial regression model, an alternative model was constructed from a reduced subset of covariates consisting of patient age and the number of oocytes retrieved.

Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

This project was conducted after internal Institutional Review Board review and approval (Montefiore IRB 2019-9899, approved 1/24/2019). Nonidentifiable patient data were obtained from the SART CORS. Patient consent was not required, as this work exclusively used retrospective data from a national registry collected during routine care.

RESULTS

Autologous fresh transfer adherence

The fresh cohort included 28,311 favorable-prognosis blastocyst transfers, of which 15,643 (55.3%) underwent eSET (Fig. 1). The 12,668 non-eSETs (44.7% of transfers) typically transferred 2 (n = 12,609 [99.5%]) and rarely 3 (n = 57) or 4 (n = 2) blastocysts.

Age, BMI, parity, maximum FSH, and AMH were clinically comparable between eSETs and non-eSETs, despite clinically small but statistically significant differences (Supplemental Table 1, available online). Non-eSETs were less likely than eSETs to be performed for unexplained (15.5% vs. 20.6%) and more likely for male factor (41.7% vs. 30.6%), endometriosis (11.4% vs. 8.9%), diminished ovarian reserve (7.3% vs. 4.9%), and tubal factor infertility (16.3% vs. 14.0%) (all $P<.001$) (Supplemental Table 2, available online).

The clinical pregnancy rate was significantly higher with non-eSET than with eSET (68.7% vs. 60.3%) (Table 1). This difference in the clinical pregnancy rate persisted after adjusting for patient age, BMI, infertility etiology, maximum FSH, AMH, and number of oocytes retrieved (adjusted difference [aD], 8.6%; 95% CI, 7.3%–10.1%, and adjusted relative risk [aRR], 1.14; 95% CI, 1.11–1.17, both $P<.001$]. The live birth rate was also significantly higher with non-eSET vs. eSET (61.6% vs. 52.7%; aD, 8.9%; 95% CI, 7.6%–10.0%, and aRR, 1.17; 95% CI, 1.14–1.21, both $P<.001$).

Of fresh eSET pregnancies, 98.2% were singletons, whereas only 55.4% non-eSET pregnancies were singleton gestations. Of live births from eSET, 96.5% were singletons, whereas only 38.0% of live births from non-eSET were singletons. Live-born infants from twin (59.5% vs. 3.5%) and triplet (2.5% vs. <0.1%) gestations were significantly increased (Table 1, all $P<.001$). The singleton rate after non-eSET remained significantly reduced after adjustment for patient age, BMI, infertility etiology, maximum FSH, AMH, and number of oocytes retrieved (aD, −43.0%; 95% CI, −44.0 to −41.7%, and aRR, 0.56; 95% CI, 0.55–0.58, both $P<.001$).

Live births from non-eSET occurred significantly earlier in gestation than births from eSET after multivariate adjustment for patient age, BMI, infertility etiology, maximum FSH, AMH, and number of oocytes retrieved (36w0d ± 22d vs. 38w0d ± 16d; aD, -11.5d; 95% CI, -12.3d to -10.7d), with far higher rates of delivery at <37 (55.0% vs. 20.1%; aD, 26.4%; 95% CI, 25.0%–27.8%, and aRR, 2.39; 95% CI, 2.27–2.52), <34 (18.7% vs. 4.9%; aD, 10.2%; 95% CI, 9.3%–11.1%, and aRR, 3.6; 95% CI, 3.1–4.2), and <28 (2.9% vs. 0.8%; aD, 2.0%; 95% CI, 1.1%–2.9%, and aRR, 3.3; 95% CI, 2.5–4.4) weeks' gestation (Table 1, all $P<.001$). Infants were also significantly more likely to be born at <2,500 g (40.1% vs. 10.6%; aD, 22.4%; 95% CI, 21.2%–23.6%, and aRR, 3.4; 95% CI, 3.1–3.7) and <1,500 g (6.2% vs. 1.7%; aD, 3.6%; 95% CI, 3.1%–4.2%, and aRR, 3.3; 95% CI, 2.7–4.1) in non-eSET births than in eSET births (Table 1, all $P<.001$).

Autologous fresh transfer adherence using the Keyhan criteria

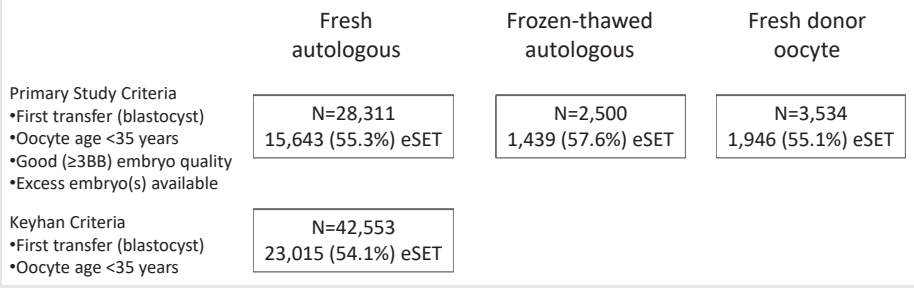
To longitudinally compare adherence between the reported guideline compliance in 2011–2012 and that in 2014–2016, we calculated eSET adherence using the criteria of Keyhan et al. (6), defined as the first autologous fresh IVF cycle in women aged <35 years undergoing blastocyst transfers. In this more loosely defined cohort of favorable-prognosis patients, 23,015 (54.1%) of 42,553 fresh transfer cycles underwent eSET (Fig. 1), consistent with the more restrictive primary fresh autologous cohort.

Autologous FET adherence

The FET cohort included 2,500 favorable-prognosis frozen-thawed blastocyst transfers, of which 1,439 (57.6%) underwent eSET (Fig. 1). Two (n = 1057 [99.6%]) and rarely 3 (n = 4), blastocysts were transferred among the 1061 (42.4%) non-eSETs.

Age, BMI, parity, maximum FSH, and AMH were clinically comparable between eSETs and non-eSETs (Supplemental Table 2), although age and BMI were slightly higher in non-eSETs. FET non-eSETs were less likely than eSETs to be performed for unexplained (11.1% vs. 15.1%, $P=.004$) and more likely for uterine (9.6% vs. 5.2%,

FIGURE 1



Cycle characteristics. The number of fresh autologous, frozen-thawed autologous, and fresh donor oocyte cycles meeting the defined inclusion criteria are shown. The number and percentage of cycles undergoing eSET are shown for each category. eSET = elective single embryo transfer.

Gingold. Adherence to embryo transfer guidelines. Fertil Steril 2021.

TABLE 1

Outcomes from fresh transfers.

	Non-eSET	eSET	Absolute difference (95% CI)	Adjusted absolute difference[a] (95% CI)	Adjusted relative risk[b] (95% CI)
No. of transfers	12,668	15,643			
Clinical pregnancy, n (%)	8,698.0 (68.7)	9,436.0 (60.3)	8.3 (7.2, 9.5)	8.6 (7.3, 10.1)	1.14 (1.11, 1.17)
Transfers resulting in live birth, n (%)	7,708.0 (61.6)	8,201.0 (52.7)	8.4 (7.3, 9.6)	8.9 (7.6, 10.0)	1.17 (1.14, 1.21)
Total live births	11,242	8,350			
Live births, n (%)					
Singleton	4,270.0 (38.0)	8,054.0 (96.5)	−58.5 (−59.7, −57.3)[c]	−43.0 (−44.1, −41.9)[c]	0.56 (0.55, 0.58)[c]
Twin	6,886.0 (59.5)	290.0 (3.5)	—	—	—
Triplet	282.0 (2.5)	6.0 (<0.1)	—	—	—
Quadruplet	4.0 (<0.1)	0 (0)	—	—	—
Gestational age (days) [weeks days], mean (SD) median (IQR)	252.1 [36w0.1d] (22.1) 256.0 (243–267)	266.4 [38w0.4d] (15.7) 269.0 (261–276)	−14.3 (−14.8, −13.8)	−11.5 (−12.3, −10.7)	NA
Delivery at < 37 weeks' GA, n (%)	3,545.0 (55.0)	1,603.0 (20.1)	34.9 (33.6, 36.2)	26.4 (25.0, 27.8)	2.39 (2.27, 2.52)
Delivery at < 34 weeks' GA, n (%)	2,103.0 (18.7)	408.0 (4.9)	13.8 (13.0, 14.7)	10.2 (9.3, 11.1)	3.6 (3.1, 4.2)
Delivery at < 28 weeks' GA, n (%)	323.0 (2.9)	66.0 (0.8)	2.1 (1.7, 2.5)	2.0 (1.1, 2.9)	3.3 (2.5, 4.4)
Birth weight (g), mean (SD) median (IQR)	2,649.0 (732.0) 2,651.0 (2,241.0–3,133.0)	3,207.0 (706.0) 3,260.0 (2,892.0–3,600.0)	−558.0 (−578.0, −537.0)	−437.0 (−466.0, −407.0)	NA
Birth weight < 2,500 g, n (%)	4,505.0 (40.1)	886.0 (10.6)	29.5 (28.3, 30.6)	22.4 (21.2, 23.6)	3.4 (3.1, 3.7)
Birth weight < 1,500 g, n (%)	700.0 (6.2)	143.0 (1.7)	4.5 (4.0, 5.0)	3.6 (3.1, 4.2)[d]	3.3 (2.7, 4.1)[d]

Note: All $P < .001$.

Note: Outcomes from fresh transfers were stratified by decision to perform eSET vs. non-eSET. The denominator for pregnancy outcomes is the number of transfers performed. The denominator for live birth outcomes is the number of live births. CI = confidence interval; eSET = elective single embryo transfer; GA = gestational age; IQR = interquartile range; NA = not available; No. = number, SD = standard deviation.

[a] Non-eSET–eSET, adjusted for patient age, body mass index, infertility etiology, maximum follicle-stimulating hormone, anti-Müllerian hormone, and number of oocytes retrieved unless otherwise noted.

[b] Non-eSET/eSET, adjusted for patient age, body mass index, infertility etiology, maximum follicle-stimulating hormone, anti-Müllerian hormone, and number of oocytes retrieved unless otherwise noted.

[c] Singleton vs. nonsingleton birth.

[d] Reduced model adjusting for patient age and number of oocytes retrieved.

Gingold. Adherence to embryo transfer guidelines. Fertil Steril 2021.

$P<.001$) or polycystic ovary syndrome (16.4% vs. 13.5%, $P=.040$) infertility (Supplemental Table 2).

The clinical pregnancy rate was significantly higher with non-eSET than with eSET (76.7% vs. 66.5%) and remained significant after adjusting for patient age, BMI, infertility etiology, maximum FSH, AMH, and number of oocytes retrieved (aD, 9.7%; 95% CI, 6.1%–13.2%, and aRR, 1.14; 95% CI, 1.09–1.20, both $P<.001$) (Table 2). The live birth rate was also significantly higher with non-eSET than with eSET (65.2% vs. 58.9%) and remained so after multivariate adjustment (aD, 6.0%; 95% CI, 2.2%–9.8%; $P=.002$, and aRR, 1.10; 95% CI, 1.03–1.17; $P=.004$) (Table 2).

Of FET live births from eSET, 95.2% were singletons, whereas only 41.9% of live births from non-eSET were singletons, with births from twin (56.9% vs. 4.8%) and triplet (1.2% vs. 0%) gestations significantly increased (Table 2, all $P<.001$). The singleton rate after non-eSET remained significantly reduced after adjustment for patient age, BMI, infertility etiology, maximum FSH, AMH, and number of oocytes retrieved (aD, -35.9%; 95% CI, -40.2 – -31.6%, and aRR, 0.69; 95% CI, 0.66–0.73, both $P<.001$).

Live births from FET non-eSET occurred significantly earlier than births from eSET after multivariate adjustment for patient age, BMI, infertility etiology, maximum FSH, AMH, and number of oocytes retrieved (35w6d ± 24d vs. 38w1d ± 17d; aD, −16.5d; 95% CI, −18.4d to −14.6d), with higher rates of delivery at <37 (56.4% vs. 19.5%; aD, 28.9%; 95% CI, 24.4%–33.4%, and aRR, 2.6; 95% CI, 2.2–3.1, both $P<.001$), <34 (22.2% vs. 4.7%; aD, 12.1%; 95% CI, 8.2%–16.0%, and aRR, 4.3; 95% CI, 3.0–6.2, both $P<.001$), and <28 (4.0% vs. 1.2%; aD, 2.3%; 95% CI, −1.0% to 5.7%; $P=.20$, and aRR, 2.9; 95% CI, 1.4–6.4; $P=.01$) weeks' gestation (Table 2). Infants were also significantly more likely to be born at <2,500 g (38.0% vs. 8.9%; aD, 22.2%; 95% CI, 18.4%–26.1%, and aRR, 3.9; 95% CI, 3.0–5.1; both $P<.001$) and <1,500 g (5.4% vs. 2.4%; aD, 2.1%; 95% CI, 0.3%–3.8%; $P=.02$, and aRR, 2.1; 95% CI, 1.8–3.8; $P=0.01$) in FET non-eSET births than in eSET births (Table 2).

Fresh donor oocyte cycle transfer adherence

The donor oocyte cohort included 3534 favorable-prognosis fresh blastocyst transfers, of which 1,946 (55.1%) underwent eSET (Fig. 1). Transfers of 2 (n = 1570 [98.8%]), 3 (n = 17 [1.1%]), and 4 (n = 1) blastocysts were reported. Donor oocyte cycles included anonymous (n = 3,192 [90.3%]), known nongenetic (n = 166 [4.7%]), known genetic relative (n = 162 [4.6%]), and female partner (n = 14 [0.4%]) cycles (Supplemental Table 3, available online). Donor cycles in which non-eSET was performed were more likely than eSET cycles to use known genetic relatives as donors (6.1% vs. 3.3%, $P<.001$) and less likely to use anonymous donors (88.3% vs. 92.0%, $P<.001$) (Supplemental Table 3).

Donor and recipient age, recipient BMI, and parity were clinically comparable between eSETs and non-eSETs, although there were small differences in recipient age, BMI, and parity (Supplemental Table 3). The largest share of donor cycles was performed for the infertility etiology of diminished ovarian reserve (74.8% of non-eSETs and 78.5% of eSETs) (Supplemental Table 3). There were small differences in the number of oocytes retrieved (22.3 [10.8] vs. 23.6 [10.4]) and number of embryos cryopreserved (4.7 [4.1] vs. 5.7 [4.1]) between non-eSET and eSET donor cycles (both $P<.001$) (Supplemental Table 3).

The clinical pregnancy rate was higher with donor cycle non-eSET than with eSET (77.6% vs. 67.4%) and remained so after adjustment for patient age, donor age, BMI, infertility etiology, and number of oocytes (aD, 10.7%; 95% CI, 7.2%–14.1%, and aRR, 1.16; 95% CI, 1.10–1.21; both $P<.001$) (Table 3). The live birth rate was also higher with non-eSET than with eSET (69.1% vs. 57.0%) and remained so after multivariate adjustment (aD, 12.3%; 95% CI, 8.6%–16.0%, and aRR, 1.25; 95% CI, 1.13–1.38, both $P<.001$) (Table 3).

Of donor oocyte FET live births from eSET, 97.3% were singletons, whereas only 31.3% of live births from non-eSET were singletons, with births from twin (67.6% vs. 2.7%) and triplet (1.1% vs. 0%) gestations significantly increased (Table 3, all $P<.001$). The singleton delivery rate was significantly reduced with non-eSET after multivariate adjustment (aD, −43.7%; 95% CI, −48.3 to −39.5%, and aRR, 0.48; 95% CI, 0.46–0.52; both $P<.001$).

Live births from donor oocyte FET non-eSET occurred significantly earlier than births from eSET (35w4d ± 23d vs. 37w6d ± 16d), and this difference remained significant after multivariate adjustment (aD, -12.3d; 95% CI, -14.5d to -10.1d; $P<.001$). After multivariate adjustment, non-eSET remained to be associated with higher rates of delivery at <37 (61.1% vs. 25.7%; aD, 31.4%; 95% CI, 23.7%–39.0%, and aRR, 2.09; 95% CI, 1.83–2.38), <34 (23.3% vs. 5.3%; aD, 13.9%; 95% CI, 10.9%–16.7%, and aRR, 3.58; 95% CI, 2.61–3.92), and <28 (3.3% vs. 0.6%; aD, 2.4%; 0.8%–5.7%, and aRR, 5.30; 95% CI, 2.20–12.79) weeks' gestation compared with eSET (Table 3, all $P<.001$). Infants were significantly more likely to be born at <2,500 g (44.3% vs. 11.7%; aD, 26.2%; 95% CI, 22.7%–33.0%, and aRR, 3.39; 95% CI, 2.81–4.07) and <1,500 g (7.6% vs. 1.9%; aD, 5.0%; 95% CI, 3.4%–6.7%, and aRR, 4.15; 95% CI, 2.55–7.03) in FET non-eSET births than eSET births after multivariate adjustment (Table 3, all $P<.001$).

DISCUSSION

This study measures adherence with the eSET guidelines in the most strictly defined national cohort of favorable-prognosis patients yet reported. In contrast to all other reported registry studies, our cohort was restricted to patients who met all possible criteria for anticipating a favorable prognosis (first transfer, age<35 years, high-quality blastocyst, and excess embryos available) rather than only some of the criteria and excluded all identifiable poor-prognosis transfers (e.g., poor embryo quality and recurrent pregnancy loss). The 44.7%, 42.6%, and 44.9% rates of non-eSET among highly favorable-prognosis patients undergoing fresh autologous, frozen-thawed autologous, and fresh donor oocyte transfers, respectively, demonstrate that non-adherence to SART guidelines among SART-reporting clinics is widespread.

TABLE 2

Outcomes from frozen-thawed transfers.

	Non-eSET	eSET	Absolute difference (95% CI)	Adjusted absolute difference[a] (95% CI)	Adjusted relative risk[b] (95% CI)
No. of transfers	1,061.0	1,439.0			
Clinical pregnancy, n (%)	814.0 (76.7)	957.0 (66.5)	10.2 (6.7, 13.7)	9.7 (6.1, 13.2)	1.14 (1.09, 1.20)
Transfers resulting in live birth, n (%)	692.0 (65.2)	847.0 (58.9)	6.4 (2.5, 10.2)	6.0 (2.2, 9.8); *P*= .002	1.10 (1.03, 1.17); *P*= .004
Total live births	978.0	868.0			
Live births, n (%)					
Singleton	410.0 (41.9)	826.0 (95.2)	−53.2 (−56.7, −49.8)[c]	−35.9 (−40.3, −31.6)[c]	0.69 (0.66, 0.73)[c]
Twin	556.0 (56.9)	42.0 (4.8)	—	—	—
Triplet	12.0 (1.2)	0 (0)	—	—	—
Quadruplet	0 (0)	0 (0)	—	—	—
Gestational age (days) [weeks days], mean (SD) median (IQR)	250.6 [35w 5.6d] (24.0) 255.0 (240.0–267.0)	267.1 [38w 1.1d] (16.7) 270.0 (262.0–277.0)	−16.5 (−18.4, −14.6)	−12.7 (−14.7, 10.7)	NA
Delivery at < 37 weeks' GA, n (%)	552.0 (56.4)	169.0 (19.5)	37.0 (32.9, 41.1)	28.9 (24.4, 33.4)	2.6 (2.2, 3.1)
Delivery at < 34 weeks' GA, n (%)	216.0 (22.1)	41.0 (4.7)	17.4 (14.4, 20.3)	12.1 (8.2, 16.0)	4.3 (3.0, 6.2)
Delivery at < 28 weeks' GA, n (%)	39.0 (4.0)	10.0 (1.2)	2.8 (1.4, 4.3)	2.3 (−1.0, 5.7) *P*= .20	2.9 (1.4, 6.4); *P*= .01
Birth weight (g), mean (SD) median (IQR)	2,712.0 (781.0) 2,721.0 (2,211.0–3,260.0)	3,322.0 (638.0) 3,402.0 (3,033.0–3,713.0)	−609.0 (−676.0, −542.0)	−461.0 (−534.0, –388.0)	NA
Birth weight < 2,500 g, n (%)	372.0 (38.0)	77.0 (8.9)	29.2 (25.6, 32.8)	22.2 (18.4, 26.1)	3.9 (3.0, 5.1)
Birth weight < 1,500 g, n (%)	53.0 (5.4)	21.0 (2.4)	3.0 (1.3, 4.8)	2.1 (0.3, 3.8); *P*= .02	2.1 (1.8, 3.8); *P*= .01

Note: All *P*< .001 except where indicated.

Note: Outcomes from frozen-thawed autologous transfers were stratified by decision to perform eSET vs. non-eSET. The denominator for pregnancy outcomes is the number of transfers performed. The denominator for live birth outcomes is the number of live births. CI = confidence interval; eSET = elective single embryo transfer; GA = gestational age; IQR = interquartile range; NA = not available; No. = number, SD = standard deviation.

[a] Non-eSET–eSET, adjusted for patient age, body mass index, infertility etiology, maximum follicle-stimulating hormone, anti-Müllerian hormone, and number of oocytes retrieved unless.

[b] Non-eSET/eSET, adjusted for patient age, body mass index, infertility etiology, maximum follicle-stimulating hormone, anti-Müllerian hormone, and number of oocytes retrieved unless otherwise noted.

[c] Singleton vs. nonsingleton birth.

Gingold. Adherence to embryo transfer guidelines. Fertil Steril 2021.

TABLE 3

Outcomes from fresh donor transfers.

	Non-eSET	eSET	Absolute difference (95% CI)	Adjusted absolute difference[a] (95% CI)	Adjusted relative risk[b] (95% CI)
No. of transfers	1,588.0	1,946.0			
Clinical pregnancy, n (%)	1,232.0 (77.6)	1,312.0 (67.4)	10.2 (7.2, 13.1)	10.7 (7.2, 14.1)	1.16 (1.10, 1.21)
Transfers resulting in live birth, n (%)	1,098.0 (69.1)	1,109.0 (57.0)	12.2 (9.0, 15.3)	12.3 (8.6, 16.0)	1.25 (1.13, 1.38)
Total live births	1,677.0	1,124.0			
Live births, n (%)					
Singleton	525.0 (31.3)	1,094.0 (97.3)	−66.0 (−68.4, −63.6)[c]	−43.7 (−48.3, −39.5)[c]	0.48 (0.46, 0.52)
Twin	1,134.0 (67.6)	30.0 (2.7)	—	—	—
Triplet	18.0 (1.1)	0 (0)	—	—	—
Quadruplet	0 (0)	0 (0)	—	—	—
Gestational age (days) [weeks days], mean (SD) median (IQR)	248.9 [35w3.9d] (22.7) 254.0 (239.0–263.0)	264.6 [37w5.6d] (15.5) 268.0 (258.0–274.0)	−15.7 (−17.2, −14.2)	−12.3 (−14.5, −10.1)	NA
Delivery at < 37 weeks' GA, n (%)	1,042.0 (61.1)	289.0 (25.7)	36.4 (33.0, 39.9)	31.4 (23.7, 39.0)	2.09 (1.83, 2.38)
Delivery at < 34 weeks' GA, n (%)	391.0 (23.3)	59.0 (5.3)	18.1 (15.7, 20.5)	13.9 (10.9, 16.7)	3.58 (2.61, 3.92)
Delivery at < 28 weeks' GA, n (%)	56.0 (3.3)	7.0 (0.6)	2.7 (1.7, 3.7)	2.4 (0.80, 5.7)	5.30 (2.20, 12.79)
Birth weight (g), mean (SD) median (IQR)	2,577.0 (736.0) 2,594.0 (2,155.0–3,033.0)	3,205.0 (652.0) 3,260.0 (2,853.0–3,629.0)	−628.0 (−682.0, −575.0)	−516.0 (−586.0, −447.0)	NA
Birth weight < 2,500 g, n (%)	742.0 (44.3)	131.0 (11.7)	32.6 (29.6, 33.6)	26.2 (22.7, 30.0)[d]	3.39 (2.81, 4.07)
Birth weight < 1,500 g, n (%)	127.0 (7.6)	21.0 (1.9)	5.7 (4.2, 7.2)	5.0 (3.4, 6.7)[d]	4.15 (2.55,7.03)

Note: All $P < .001$.

Note: Outcomes from fresh donor transfers were stratified by decision to perform eSET vs. non-eSET. The denominator for pregnancy outcomes is the number of transfers performed. The denominator for live birth outcomes is the number of live births. CI = confidence interval; eSET = elective single embryo transfer; GA = gestational age; IQR = interquartile range; NA = not available; No = number, SD = standard deviation.

[a] Non-eSET–eSET, adjusted for patient age, donor age, body mass index, infertility etiology, and number of oocytes retrieved unless otherwise noted otherwise.

[b] Non-eSET/eSET, adjusted for patient age, donor age, body mass index, infertility etiology, and number of oocytes retrieved.

[c] Singleton vs. nonsingleton birth.

[d] Reduced model adjusting for donor age and number of oocytes retrieved.

Gingold. Adherence to embryo transfer guidelines. Fertil Steril 2021.

Nonadherence does not necessarily imply inappropriate medical decision-making for all identified nonadherent transfers because clinical practice guidelines are only intended to guide, not dictate, care. A select minority of these patients may be plausible candidates for non-eSET for reasons not evident in the registry. Care decisions should ideally be driven by a shared decision-making process guided by expert advice and individualized for the patient (10), and decisions at variance with guidelines may be completely appropriate in context.

The justifications for nonadherence among these favorable-prognosis patients cannot be identified from this registry, although several plausible reasons likely exist. Patient desires to achieve a pregnancy as quickly as possible likely factor into the decision to transfer excess embryos, as non-eSET remains associated with a higher pregnancy rate per transfer. Many patients struggling with infertility likely underappreciate the risks associated with multifetal gestation. Many other patients, particularly those with limited or no insurance coverage of infertility treatments, have a significant financial incentive to avoid additional embryology and monitoring fees associated with subsequent frozen embryo transfers, even if non-eSET results in significant additional costs to the health system.

Indeed, a cost analysis model comparing a simulated cohort of US military patients who either underwent sequential single embryo transfer (SET) or dual embryo transfer demonstrated that a SET strategy would be less costly after accounting for maternal and neonatal care (10). Multiple studies from Belgium and other European countries also demonstrate the safety and cost-effectiveness of a strict SET policy via a dramatic reduction in multiple pregnancies (11–14). Encouragingly, improvements in the SET rate are possible even without eSET mandates. A systematic review found that patient education about the risks of multiple pregnancies and non-eSETs increased patient eSET acceptance and use (15).

While no studies to date have reported on the familiarity of practicing reproductive endocrinologists with current guidelines for the number of embryos to transfers, some nonadherence may also stem from limited awareness among healthcare professionals. Outreach efforts from professional societies remain critical in facilitating the adoption of guidelines into daily practice. Public grading of clinics on the CDC or SART websites on the basis of the adherence rates or tying of insurance payments for IVF to mandatory eSET may also play a significant role in facilitating broader adoption of eSET in practice.

Overall, these results suggest that IVF practices nationally have made dramatic improvements since 2011–2012, when 71% and 72% nonadherence rates were reported for fresh autologous and fresh donor oocyte transfers, respectively (6, 16), but that a large gap persists between guidelines and practice.

Despite our efforts to identify the most favorable-prognosis patients, some patients from the registry may have been inaccurately categorized. While this study excluded patients who reported any prior IVF cycles with transfers, whether fresh or frozen-thawed, the reliability of this field in the SART CORS registry is limited because it relies on patient and clinic self-reporting. Because individual patients in the registry are not identified and tracked across participating clinics, patients undergoing their first IVF cycle at 1 clinic may still have had a previous unsuccessful cycle at another site that was not disclosed or reported to the SART.

Although this study was restricted to patients whose best embryo transferred was high quality (3BB or better), the limited embryo quality categories in the SART CORS registry, grouping all 3BB or better embryos as "good," preclude determining whether non-eSET was more likely to be performed for certain grades. Moreover, the second embryo, if transferred fresh, may not have been of sufficient quality for cryopreservation. Thus, eSET patients who cryopreserved excess embryos are not precisely matched to non-eSET patients, some of whom may have undergone fresh transfer of "excess" embryos not fit for cryopreservation, rather than discard them. Nonetheless, the retrieval of >15 oocytes on average in the fresh autologous population (Supplemental Table 1) suggests that patients with embryos unsuitable for cryopreservation but suitable for fresh transfer are uncommon.

While cycles entailing PGT were explicitly excluded among frozen transfers, such cycles were represented among the fresh transfers. Among first fresh autologous cycles, 640 (2.3%) were labeled as using PGT for some or all of the embryos. However, the implications of this label are unclear, as such cycles likely entailed fresh transfer of an untested embryo, with testing and cryopreservation of the remaining embryos for use in frozen-thawed cycles. Moreover, the effect sizes in this study far exceeded the maximum possible representation of PGT cycles in the fresh cohorts.

The improved clinical pregnancy and live birth rates with FETs compared with those with fresh embryo transfers in favorable-prognosis women aged <35 years are consistent with prior registry data demonstrating a benefit with FET among high responders undergoing their first autologous cycle (17), a subset well represented within our young cohort.

The live birth rates per transfer were 52.7% for the first fresh embryo and 58.9% for the first frozen-thawed embryo when eSET was performed, whereas the marginal improvement in the live birth rate from transfer of >1 embryo in either fresh or frozen-thawed cycles was only approximately 8%, far less than would have been expected if the excess embryos were cryopreserved and transferred in a subsequent cycle.

One study using CDC ART surveillance data of 14,398 women aged <35 years undergoing their first fresh transfer and with cryopreservation of at least 1 embryo estimated that approximately 36% of patients without a live birth after their fresh eSET would achieve it after their second eSET in a FET cycle and almost all of these would be singleton pregnancies (18). The projected cumulative live birth rate after such a sequential strategy was 68%, compared with 57.7% for the dual embryo transfer strategy (18).

The findings from our SART registry data suggesting a less-than-expected benefit from non-eSET, as well as CDC registry data suggesting an improvement in cumulative live birth rate with a sequential SET strategy, underline the importance of optimizing the endometrium before any transfer. This is likely one of the most significant remaining modifiable

factors among favorable-prognosis patients because embryonic factors are frequently already near optimal.

The analysis of fresh donor oocyte cycles yielded similar findings to autologous cycles, with non-SETs still representing a sizable minority of transfers. Higher rates of prematurity and low birth weight in association with dramatically increased multiple pregnancy rates were confirmed in non-SET compared with SET donor oocyte cycles. The total complications and costs of these (as well as autologous IVF) non-eSET pregnancies are incompletely captured because of the limited number of fields available in the SART database.

Multiple gestation pregnancies are associated with higher rates of preeclampsia, gestational diabetes, placental abruption, and intrauterine fetal demise (19–22), and high rates of multifetal gestation were observed in association with non-eSETs among fresh autologous, frozen-thawed autologous, and fresh donor oocyte cycles. While there were some small but statistically significant baseline differences between patients undergoing eSET and those undergoing non-eSET, these covariates could not adequately explain the large differences between transfer outcomes. Indeed, the adjusted absolute differences for all outcomes were nearly identical to the unadjusted absolute differences.

The substantial risks of iatrogenic prematurity and low-birth-weight infants in association with non-eSET are also evident in this study. Importantly, extremely premature (<28 weeks) and very-low-birth-weight (<1,500 g) infants, who are at the highest risk of severe, long-term morbidity, are also markedly more frequent with non-eSET than with eSET (Tables 1 and 2).

These effects are likely exacerbated among the donor oocyte cycles (Table 3). Advanced maternal age is also strongly associated with preeclampsia, gestational diabetes, placental abruption, and intrauterine fetal demise (23–25). Given that the mean donor oocyte recipient age was 41 years and the non-eSETs incurred a high rate of multifetal gestation, we suspect that these obstetric complications, although not available within the SART registry, were likely very common among pregnancies resulting from donor oocyte non-eSETs.

Although our study excluded patients with a prior live birth from ART and instead focused on the first transfers, future studies may be able to validate our findings in this additional favorable-prognosis patient cohort. The SART database has included a field recording prior ART live births since 2016, significantly simplifying future analyses on this question.

This work reinforces the well-established neonatal implications of performing transfers in excess of recommendations designed to minimize multiple pregnancies (1, 2). Almost all multiple gestations leading to a live birth in the fresh cohort (3,538/3,685 [96.0%]) were a consequence of non-eSET, suggesting that non-eSET was also responsible for a large share of obstetric morbidity.

In conclusion, our SART registry study confirms that even among the most strictly defined cohort of favorable-prognosis patients undergoing autologous blastocyst transfer, nonadherence to the ASRM guidelines is common, despite improvements since 2012. Obstetric and neonatal morbidity remains a significant associated complication of non-eSET among favorable-prognosis patients. Additional policies and incentives to promote singleton pregnancies among patients undergoing IVF may be critical to further narrowing this gap in practice adherence.

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Adherencia a las recomendaciones para transferencias embrionarias en pacientes menores de 35 años con pronóstico favorable utilizando ovocitos propios y en receptoras de ovocitos donados: estudio de notificación de resultados clínicos de la "Society for Assisted Reproductive Technology".

Objetivo: Medir las consecuencias del no seguimiento de las recomendaciones de 2013 de la American Society for Reproductive Medicine de transferencia electiva de un único embrión (eSET) en las pacientes de buen pronóstico.

Diseño: Cohorte retrospectiva.

Entorno: Clínicas de fecundación in vitro.

Paciente(s): Un total de 28,311 ciclos de fecundación in vitro de ovocitos propios en fresco, 2,500 ciclos de transferencia de congelados propios y 3,534 ciclos de donación de ovocitos en fresco de los centros que comunicaron sus datos a la Society for Assisted Reproductive Technology entre 2014 y 2016.

Intervención(es): Pacientes < 35 años o que utilizaron ovocitos donados < 35 años sometidas a la primera transferencia de un blastocisto.

Medida del resultado principal: Tasa de nacidos únicos, edad gestacional en el parto y peso al nacer comparados entre los grupos de e-SET y no e-SET utilizando el test de chi-cuadrado o el test exacto de Fisher o t-tests.