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ASSISTED REPRODUCTION TECHNOLOGIES

Guidance for elective single-embryo transfer should be applied to frozen embryo transfer cycles

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Abstract

Purpose To provide clinicians with data showing the benefits of transferring a single blastocyst in frozen embryo transfer (FET) cycles so that they may counsel their patients accordingly.

Methods This is a closed cohort study of 678 FET cycles occurring between January 2011 and December 2017 in a private IVF laboratory and associated physicians' practice. Patients included in the analysis were less than 38 years of age at oocyte collection, had at least two vitrified blastocysts, and were undergoing their first autologous FET cycle. The patients were categorized into four groups after they had chosen either elective single-embryo transfer (eSET) or double-embryo transfer (eDET). Outcomes for eSET and eDET were compared within groups of patients having freeze-all IVF cycles (PGT-A patient vs. non-PGT-A patient) and fresh IVF transfer groups (negative outcome vs. pregnant/delivered in fresh cycle). Main outcome measures of the study were live birth, multiple pregnancy, and implantation rates.

Results There were no statistically significant differences observed in live birth rates for eSET (54–62%) vs. eDET (54–66%) ($P = 0.696$–1.000) in the four patient groups evaluated. Multiple pregnancy rates were significantly decreased in all eSET groups (0–3%), compared with eDET groups (24–65%) ($P = 0.0001$–0.037).

Conclusions This data shows that transfer of a single vitrified-warmed blastocyst maintains live birth rates, while decreasing multiple pregnancies, and may become more acceptable to physicians and patients.

Keywords Frozen embryo transfer · FET · Single-embryo transfer · eSET · IVF

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Introduction

Success rates for in vitro fertilization/embryo transfer (IVF/ET) have dramatically improved since the first reported birth from IVF/ET in 1978. Initially, the standard practice was to transfer multiple embryos to overcome the inherent inefficiencies of assisted human reproduction. While this did enhance pregnancy rates, it was accompanied by a marked increase in both twin and other high-order multiple births. With a higher rate of multiple births came a commensurate rise in complications for both the mother and the infants [1–4]. It has also been shown that ART-conceived twins are at greater risk for pregnancy complications and adverse perinatal outcome than non-ART-conceived twins [5]. Furthermore, this led to an escalation in healthcare costs, in large part, due to the lengthy stay in the neonatal intensive care unit required for babies born either preterm or very preterm [6–8].

Since the majority of multiple gestations in IVF/ET result from the transfer of more than one embryo, the Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) developed guidance for the number of embryos to transfer. The initial guidance was developed in 1998 for cleavage-stage embryo transfer and was updated six times between 1999 and 2013 [9–11]. The guidance was developed to address the increasing number of twins and high-order multiples that IVF programs were reporting to SART and to recommend a maximum number of embryos to transfer according to the patients' age, quality of the embryos, and other favorable prognostic factors. Single-embryo transfer was first recommended in 2004 [9]. The recommendation was for patients < 35 years old to have an elective single-embryo transfer (eSET) if the patient had characteristics associated with a good prognosis. These characteristics include (1) first IVF cycle or successful pregnancy through a previous IVF cycle, (2) good-quality embryos, as graded by morphological examination, and (3) embryos of sufficient quality, in excess of those transferred, that could be cryopreserved. This guidance applied to fresh embryo transfers. Additional recommendations were made for patients in age groups 35–37, 38–40, 41–42, and > 43. The most recent update, in 2017 [12], also made a recommendation for the transfer of a single euploid embryo in all age groups and other vitrified day-5 or day-6 embryos in < 35 and 35–37-year-old patients in frozen embryo transfer (FET) cycles.

In our experience, when patients are successful with eSET in their initial IVF cycle, they and their clinicians will elect SET for their FET cycle. Conversely, when patients are unsuccessful with eSET in their initial IVF cycle, they and their clinicians are more likely to elect double-embryo transfer (DET). Therefore, the aim of this study was to provide clinicians with data showing the benefits of transferring a single blastocyst in a frozen embryo transfer cycle so that they may counsel their patients accordingly.

Materials and methods

Study design

A closed cohort design was utilized in this study. This is appropriate when (1) a defined number of persons are studied (678 patients), (2) the group of persons that comprise the cohort are characterized (< 38 years old at the time of oocyte collection, having at least two vitrified blastocysts in storage and their first FET during the study time period, and (3) the study time period is specified (between January 2011 and December 2017) [13].

The clinical pregnancy, live birth, multiple pregnancy, and implantation rates (number of gestational sacs (GS)/number of embryos transferred) of all patients in the cohort were analyzed. To determine if preimplantation genetic testing or previous success or failure after fresh IVF transfer altered cycle results, FET outcomes were evaluated according to the patients' election to have preimplantation genetic testing or not (PGT-A patient; non-PGT-A patient) as well as the fresh IVF/ET cycle outcome in the group of patients with an embryo transfer in their IVF cycle (negative outcome; pregnant and delivered in fresh cycle).

Prior to their FET cycle, the clinical staff discussed the risks and benefits involved with the transfer of one versus two embryos, with an emphasis on the chance of multiple gestation. In addition, the risks associated with multiple gestation for both the mother and the fetus were discussed and the patients self-elected either SET or DET for their FET cycle.

A total of 678 FET cycles in all patients who met the eSET study criteria were analyzed. The mean age of the patients at the time of egg retrieval was compared among the four groups. FET outcomes were compared within two major groups of patients: in patients that did not have a fresh IVF cycle transfer, outcomes were evaluated according to the patients' election to have PGT-A or not. In patients that had a fresh IVF-ET cycle transfer, outcomes were evaluated according to their fresh cycle outcomes (Table 1). Follow-up time for the study concluded with a negative pregnancy test for non-pregnant patients, and at notification of birth for pregnant patients.

Ovarian stimulation and egg retrieval

Ovarian stimulation included either follicle stimulating hormone (FSH) or combination FSH/human menopausal gonadotropin (HMG) in gonadotropin-releasing hormone (GnRH) agonist or antagonist protocols. The decision for which protocol to use for ovarian hyperstimulation was made by the patient's primary physician. Final oocyte maturation was achieved with a subcutaneous injection of either human chorionic gonadotropin (hCG) (500 micrograms (mcg) or 375 mcg for high responders) or leuprolide acetate (antagonist cycles only, 4 mg). The time of the hCG or leuprolide acetate injection was determined after documenting adequate follicular development by transvaginal ultrasound and rising serum estradiol (E2) levels. Ultrasound-guided transvaginal oocyte retrieval was performed 35 h after the injection of hCG or leuprolide acetate.

Fertilization, culture, and blastocyst vitrification

Oocytes were fertilized using conventional insemination or intracytoplasmic sperm injection (ICSI) and were cultured for up to 5 days before embryo transfer and 5–6 days before vitrification. Vitrification and warming were done by a procedure previously described [14]. The vitrification procedure did not change over the time of the study.

Table 1 Comparison of eSET vs. eDET in four groups of patients having 678 FET cycles occurring between January 2011 and December 2017

	FET for Patients having no Fresh IVF cycle transfer				FET subsequent to a Fresh IVF cycle transfer				All Patients *n*=678	
	PGT-A patients *n*=269		Non-PGT-A patients *n*=113		Negative, biochemical, or miscarriage in fresh cycle *n*=200		Pregnant & delivered in fresh cycle *n*=96			
	eSET	eDET	eSET	eDET	eSET	eDET	eSET	eDET	eSET	eDET
No. of transfers	239 (89)	30 (11)	66 (58)	47 (42)	28 (14)	172 (86)	54 (56)	42 (44)	387 (57)	291 (43)
Average age at oocyte retrieval	32.8[a]	31.5[a]	30.2[e]	31.9[e]	30.3[i]	31.4[i]	30.2[m]	31.3[m]	31.8[q]	31.4[q]
Live birth (%)	133 (56)[b]	17 (57)[b]	41 (62)[f]	31 (66)[f]	15 (54)[j]	93 (54)[j]	30 (56)[n]	25 (60)[n]	219 (57)[r]	166 (57)[r]
No. of multiple (%)	0[c]	11 (65)[c]	1 (2)[g]	14 (45)[g]	0[k]	22 (24)[k]	1 (3)[o]	7 (28)[o]	2 (0.5)[s]	54 (33)[s]
Implantation rate (No. of GS/No. embryos transferred) (%)	152/239 (64)[d]	34/60 (57)[d]	45/66 (68)[h]	57/94 (61)[h]	15/28 (54)[l]	148/344 (43)[l]	34/54 (63)[p]	39/84 (46)[p]	246/387 (64)[t]	278/582 (48)[t]

With the exception of patient ages, values represent n (%). Ages between patient groups were compared using Unpaired t Test, all others were compared using Fisher's Exact Test. P<0.05 was considered to be significant

[a] P= 0.037, [b] P=1.000, [c] P= 0.0001, [d] P= 0.372, [e] P=0.006, [f] P= 0.696, [g] P=0.0001, [h] P=0.404, [i] P= 0.110, [j] P= 1.000, [k] P=0.037, [l] P=0.324, [m] P= 0.067, [n] P=0.835, [o] P= 0.017, [p] P=0.080, [q] P=0.239, [r] P=0.937, [s] P= 0.0001, [t] P=0.0001

Embryo quality scoring

Blastocyst-stage embryos were graded for expansion and quality of the trophectoderm and inner cell mass after warming and re-expansion according to the method described by Schoolcraft et al. [15]. For data analysis, the number of good-quality embryos transferred in each study group was compared (Table 2). Blastocysts were considered of good quality if their expansion/hatching status was stage 2–6, and ICM/TE were grade A or B (example: 4AA, 3AB, 5BB, etc.).

Frozen embryo transfer

FETs were done in either a natural cycle or a hormone replacement cycle (HRT). For natural cycles, the patient was given a 250-mcg hCG injection when a mature follicle and adequate endometrium were verified by transvaginal ultrasonography. Progesterone supplementation (progesterone in oil injection, Crinone vaginal gel, or oral progesterone tablet) commenced 2 days later. FET occurred 1 week after the hCG injection. For HRT cycles, patients received estrogen supplementation (oral estrogen tablet, estradiol valerate injection, or estrogen patch) and started progesterone (progesterone in oil injection) when the serum estradiol level was above 250 pg/ml and an adequate endometrium was verified by transvaginal ultrasonography. FET was scheduled on the sixth day of progesterone supplementation. All embryo transfers were performed using transabdominal ultrasound guidance.

Pregnancy was determined by measuring serum beta-hCG levels starting 10–12 days after embryo transfer using a Beckman-Coulter Access2 analyzer, and then every 2–3 days until appropriately rising levels were confirmed. Clinical pregnancy was confirmed with transvaginal ultrasound at approximately 6–10 weeks of gestation. Live birth information was obtained either directly from the patient or from their obstetrician. Since the CDC and SART require reporting of births, there was no missing data.

Statistical analysis

Statistical analysis was done using GraphPad Prism. Proportion data were analyzed using Fisher's exact test; age differences between patient groups were compared using unpaired *t* test. $P < 0.05$ was considered to be statistically significant.

Institutional review board

A retrospective chart review was performed with the use of a secure electronic database of patients' IVF and FET cycles. No protected health information was utilized during the chart review. The Institutional Review Board determined that this study does not constitute human subjects research and does not appear to be in violation of any human subject protections.

Table 2 Proportion of patients with zero, one, or two good-quality blastocysts transferred in each study group

	FET for patients having no fresh IVF cycle transfer				FET subsequent to a fresh IVF cycle transfer				All patients $n = 678$	
	PGT-A patients $n = 269$		Non-PGT-A patients $n = 113$		Negative, biochemical, or miscarriage in fresh cycle $n = 200$		Pregnant and delivered in fresh cycle $n = 96$			
	eSET	eDET	eSET	eDET	eSET	eDET	eSET	eDET	eSET	eDET
No. of transfers	239	30	66	47	28	172	54	42	387	291
Transfer of 0 good-quality embryos (%)	34 (14)[a]	4 (13)[a]	14 (21)[b]	5 (11)[b]	2 (7)[c]	21 (12)[c]	13 (24)[d]	7 (16)[d]	63 (16)[e]	37 (13)[e]
Transfer of 1 good-quality embryo (%)	205 (86)	7 (23)	52 (79)	19 (40)	26 (93)	78 (45)	41 (76)	20 (48)	324 (84)	124 (43)
Transfer of 2 good-quality embryos (%)	0	19 (63)	0	23 (49)	0	73 (42)	0	15 (36)	0	130 (45)
No. of good-quality blastocysts transferred (Ave.)	205 (0.86)[f]	45 (1.50)[f]	52 (0.79)[g]	65 (1.38)[g]	26 (0.93)[h]	224 (1.3)[h]	41 (0.76)[i]	50 (1.19)[i]	324 (0.84)[j]	384 (1.32)[j]

Differences between patient groups were compared using Fisher's exact test. $P < 0.05$ was considered to be significant. [a] $P = 0.665$, [b] $P = 0.202$, [c] $P = 0.744$, [d] $P = 0.609$, [e] $P = 0.151$, [f] $P < 0.0001$, [g] $P < 0.0001$, [h] $P = 0.0048$, [i] $P = 0.0004$, [j] $P < 0.0001$

Results

Patient ages ranged from 23 to 37 at the time of their oocyte retrieval with an average age of 31.7 years. When differences in patient ages between eSET and elective double-embryo transfer (eDET) for the four study groups were compared, patients electing SET in the PGT-A group were significantly older, while patients electing SET in the non-PGT-A group were significantly younger. While these results were statistically significant, they were small and unlikely to be clinically significant. All other age comparisons showed no significant differences including the summary of all eSET and eDET patients (Table 1).

Patients self-elected either eSET or eDET for their FET cycle and showed a preference for either eSET or eDET according to their study group. Of the 269 patients who had PGT-A, 89% chose eSET over eDET while just 58% of patients without PGT-A chose eSET. Of 200 patients that delivered following their fresh IVF cycle, 56% chose eSET while only 14% of patients with an unsuccessful fresh IVF cycle chose eSET (Tables 1 and 2). Overall, 57% of the patients in the study chose eSET and 43% chose eDET.

The number of good-quality blastocysts transferred in each cycle was compared between eSET and eDET for the four study groups (Table 2). There were no significant differences in the number of transfers having at least one good-quality blastocyst transferred in any of the comparisons. However, with the transfer of a second embryo in DET cycles, the average number of good-quality embryos transferred was significantly higher for eDET (1.19–1.50) than eSET (0.76–0.93) ($P = 0.0048$–$P < 0.0001$) for all study groups.

Clinical pregnancy and live birth rates appeared slightly higher for patients with eDET compared with eSET; however, these differences did not reach statistical significance. Implantation rates were slightly higher for eSET compared with eDET in all four patient groups, but the differences reached statistical significance only in the summary of all eSET and eDET patients. On the other hand, multiple pregnancy rate was statistically higher with eDET in all four comparisons, with eDET having 24–65% multiples compared with eSET having 0–3% multiples (monozygotic twins) across the four patient groups ($P = 0.037$–$P < 0.0001$) (Table 1).

Discussion

Design and outcome

This study is limited by its lack of randomization of eSET vs. eDET and its retrospective design as well as the small numbers in each group. Even though this is not a randomized trial, it provides valuable information for clinicians who are counseling their patients regarding the number of cryopreserved embryos to thaw and transfer in each cycle. In addition, multiple stimulation protocols were utilized in the initial IVF cycle at the discretion of the patient's physician. Since the results of the study are based on the outcome of blastocyst transfers in an FET cycle, and not the number of oocytes retrieved, the particular stimulation protocol for the IVF cycle should have minimal effect on the outcome. Furthermore, the different protocols are seen across all four groups of patients.

Another limitation of our study is that we evaluated live birth but did not evaluate complications associated with the pregnancies for the mother and infant. Multiple studies have documented the range of complications associated with multiple gestation in ART pregnancies. These complications include placenta previa [2], gestational diabetes [4], gestational hypertension/pre-eclampsia [3, 4], premature rupture of the membranes [4], elective Cesarean delivery [2], preterm and very preterm birth [2, 4], low birth weight [2, 4], very low birth weight [4], and congenital malformations [2, 4]. In fact, Daniel et al. [5] concluded that ART-conceived twin pregnancies are at even greater risk than non-ART-conceived ones for pregnancy complications and adverse perinatal outcome. Martin et al. [16] evaluated perinatal outcomes among singletons after assisted reproductive technology that resulted from single-embryo or double-embryo transfer and compared these pregnancies with singletons conceived without ART. When they compared non-ART singleton pregnancies with singletons born after both eSET and non-elective SET, they found no increased risk. However, when they looked at pregnancies after double-embryo transfers, even the singleton pregnancies had higher risks. They concluded that the increased risks of poor perinatal outcome among singleton pregnancies after ART were limited to those conceived after double-embryo transfer. This study suggests that just the transfer of more than one embryo, even if it results in a singleton pregnancy, has increased risks of poor perinatal outcome. Since there are many studies documenting adverse outcomes associated with multiple gestation in ART pregnancies, the primary focus of our study was to provide information to clinicians that would support the transfer of a single blastocyst in FET cycles.

Elective single-embryo transfer, especially in FET cycles, has historically been avoided if at least two cryopreserved embryos were available. Concerns about the decreased implantation potential of cryopreserved embryos made physicians hesitant to transfer less than two embryos in an FET cycle. This policy primarily originated from the practice of transferring the best embryos in the fresh cycle and then cryopreserving the remaining embryos, which may have been of lesser quality. In addition, older cryopreservation techniques yielded lower survival and implantation rates than are currently seen with the advent of blastocyst vitrification [17]. Another major barrier to the clinic's acceptance of eSET is the patient's strong desire for the transfer of more than one embryo. This is influenced by many factors including the patient's length of infertility, financial situation, and lack of knowledge, or discounting the risks and complications, of multiple pregnancy and birth [18].

This study shows that across all groups, live birth rates with DET were equivalent or slightly higher that eSET, although this was not statistically significant (Table 1). While some studies have shown statistically higher pregnancy rates with DET [19], others have shown similar pregnancy rates when comparing eSET with eDET [20, 21]. However, these studies do consistently show a marked increase in multiple gestation with eDET. The reason for equivalent pregnancy rates in our study may be due to embryo quality (if the embryo quality is not excellent, the physician may be more inclined to transfer an extra embryo) or may be related to other factors such as endometrial receptivity or body mass index which were not evaluated in this study. There could also be other patient-factors that we have not identified, such as endometrial development, that may also influence the decision for performing DET.

When we evaluated embryo quality, the number of cycles with at least one good-quality embryo transferred showed no significant difference. However, with the transfer of a second embryo in DET cycles, the average number of good-quality embryos transferred was significantly higher for eDET compared with eSET cycles (Table 2). Our data shows that the only result of transferring the extra embryo was an increase in the multiple birth rate. However, it should be noted that, even when an embryo of lesser quality is transferred either with a single good-quality embryo, or with another lesser-quality embryo, multiple births can result. This further supports the transfer of a single blastocyst in FET cycles. With the known increase in complications for both the mother and fetus in a multiple gestation, the goal of any ART program should be to reduce the multiple birth rate while maintaining the live birth rate.

We have observed a predilection to increase the number of embryos transferred in an FET cycle following an unsuccessful IVF cycle. However, our data show equal chances of live birth with eSET and eDET in FET, whether the fresh IVF cycle was successful or not, but a significant increase in multiple pregnancy with eDET. This suggests that the transfer outcome of the initial fresh cycle has no impact on the success of the vitrified-warmed cycle and should not discourage the physician and patient from electing a single-embryo transfer. This is supported by Berin et al. [22], who reported their clinical outcomes with single- and double-blastocyst transfers. Their data showed that achieving a live birth in the fresh cycle, from which the frozen embryos resulted, was not associated with successful live birth in the frozen cycle. On the contrary, if the fresh cycle was not successful, transferring two blastocysts in the vitrified-warmed cycle resulted in a nonsignificant increase in the live birth rate but a significant increase in the twin live birth rate. Likewise, in freeze-only cycles, where no fresh IVF transfer was performed, we observed the greatest occurrence of twins (65%) with the transfer of two blastocysts in the group of patients with PGT-A. However, it should be noted that 89% of patients in this group elected SET compared with 58% of patients that did not have PGT-A. Therefore, the outcome of the fresh IVF transfer or whether PGT-A was performed or not should not alter the recommendation for the transfer of a single vitrified blastocyst if all other criteria for eSET are met.

Findings of previous studies

SART has an ongoing effort to encourage the use of elective single-embryo transfer in good prognosis patients undergoing fresh embryo transfer since twin and other high-order multiple gestations are a major complication of IVF/ET. Consequently, the occurrence of eSET in fresh IVF transfers in patients less than 35 years of age has increased more than 71 times over the last 13 years from a low of 0.7% of transfers in 2003 to 50.1% of transfers in 2016 [23] (Fig. 1). As shown in Fig. 1, the percent of eSET in IVF cycles has also increased dramatically in our practice. However, elective SET in FET cycles has been more difficult for physicians and patients to adopt.

A more recent effort has been made by SART to encourage eSET in FET cycles. In the 2013 guidance [11], they recommended not exceeding the number of good-quality fresh embryos transferred for each age group when transferring vitrified-warmed embryos. The 2017 guidance [12] went a step further with the recommendation of eSET for all euploid embryos, fresh or thawed, and for patients' first FET cycles. With the publication of the SART National Summary Report for cycles reported for 2014 and subsequent years [23], the trend in eSET can be tracked with the addition of percent of eSET in FET cycles. For example, the 2014 primary outcome data for patients less than 35 years of age showed that 33.6% involved an eSET in their fresh cycle, whereas the rate of eSET in the subsequent FET cycles followed closely at 31.2%. The rate of eSET in FET continued to increase in 2015 and 2016 with 39.3% and 45.4%, respectively [23].

Increasing the rate of eSET, thereby decreasing the average number of embryos transferred, in both fresh and frozen embryo transfers translates into a decrease in preterm and very preterm births [23]. SART defines term delivery as > 37-week gestation, preterm as delivery between 32- and 37-week gestation and very preterm as delivery < 32-week gestation. The preterm and very preterm births reported for 2016 [23] in patients < 35 years old were almost exclusively in patients receiving 2–3 + embryos. Those with 2 embryos transferred had 12.7% preterm and 2.9% very preterm, while those with 3 + embryos transferred had 7.4% preterm and 2.0% very preterm. In contrast, eSET patients had 4.3% preterm and 1.0% very preterm deliveries. These data show that the transfer of more than one embryo resulted in 2–3 times increase in preterm and very preterm birth compared with that seen after the transfer of a single embryo.

It is well known that multiple gestations result in increasing morbidity and mortality for both the mother and the infants. While the mother is at increased risk of complications in pregnancy, such as gestational diabetes and hypertension, the infants are at risk of complications primarily related to preterm and very preterm delivery [1]. Associated with the increased medical complications is an escalation in healthcare costs. Lemos et al. [6] estimated that the average total cost for mother and infant after a singleton delivery was $21,458, while twins were estimated at $104,831, and higher-order multiples were estimated at $407,199. Additionally, Lee et al. [7] estimated that the cumulative cost savings to the US healthcare system for the decrease in the number of high-order multiple (HOM) births that have occurred since the initial SART guidelines on the number of embryos transferred was published in 1998 is more than US$6 billion. However, they found that the decrease in HOM births during this time period was not accompanied by a decrease in the twin rate. They suggest an additional $2B may be saved annually with the continued reduction in iatrogenic twins [7]. Crawford et al. [8] also examined the costs of achieving live birth from ART. They compared sequential single- and double-embryo transfers and concluded that sequential SET can reduce total ART treatment and pregnancy/infant-associated medical costs by reducing multiple births without lowering live birth rates. With the increased morbidity and mortality associated with multiple gestations, as well as the rise in health care costs, physicians must

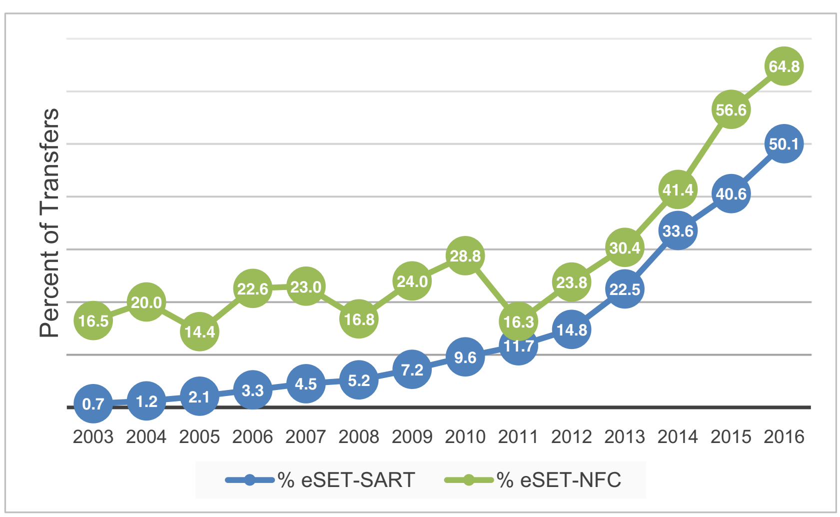

Fig. 1 Proportion of eSET in primary (fresh) IVF cycle embryo transfers according to SART data and Nashville Fertility Center (NFC) data from 2003 to 2016

be diligent in limiting the incidence of multiple births, especially where this can be controlled, in large part, by the number of embryos transferred into patients undergoing FET cycles.

In conclusion, our data do not support DET in any of our study groups of patients less than 38 years of age, even for those who had a negative outcome following their fresh embryo transfer. Though these patients are more likely to prefer DET [24], and their clinicians are more likely to recommend DET over SET, they have similar pregnancy rates in their subsequent FET cycle with eSET compared with eDET, while having significantly lower multiple pregnancy rates with eSET. Therefore, in patients less than 38 years of age, similar ongoing pregnancy and live birth rates can be maintained while reducing the occurrence of multiple gestations with eSET compared with eDET in vitrified-warmed ET cycles. This is particularly important since fewer fresh embryo transfers are being performed due to the increase in PGT-A and the observation that the rate of implantation might actually be higher in FET cycles than in fresh cycles, which may be at least partially due to the high estradiol levels seen in stimulated cycles and the possible adverse effect this might have on the endometrium [25]. If two or more cryopreserved blastocysts are available, eSET in FET cycles will also provide additional future FET attempts while decreasing complications from multiple pregnancy and possible fetal loss. Furthermore, eSET represents a significant potential cost savings since estimates for delivery of twins are as much as five times, and triplets are as much as 20 times the cost of delivery of a singleton [6].

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For retrospective studies, formal consent is not required.

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