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Experience with a patient-friendly, mandatory, single-blastocyst transfer policy: the power of one

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Abstract

Objective—To determine whether a mandatory single-blastocyst transfer (mSBT) algorithm reduced multiple gestation rates without sacrificing clinical pregnancy rates.

Design—Retrospective review.

Setting—U.S. university-based assisted reproductive technology (ART) program.

Patient(s)—All women younger than 38 years undergoing their first ART cycle from 2009 to 2010 with 4 high-grade embryos on day 3 after oocyte retrieval (patients from 2009 were the “before” group, and patients completing ART under the mSBT policy in 2010 were the “after” group).

Intervention(s)—mSBT algorithm.

Main Outcome Measure(s)—Multiple gestation and clinical pregnancy rates.

Result(s)—Of the qualified patients, 136 women met inclusion criteria (62 from 2009, 74 from 2010). The baseline demographics were similar between the groups. Statistically significantly fewer blastocysts were transferred per patient in 2010 compared with 2009 (1.5 vs. 1.9). The clinical pregnancy rates before (67.7%) or after (63.5%) the mSBT policy were not statistically significantly different. Multiple gestation rates were statistically significantly reduced, from 43.8% (2009) to 14.6% (2010) after the mSBT policy was instituted. More patients from 2010 had 1 blastocyst cryopreserved compared with 2009 (52.9% vs. 30.6%).

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Conclusion(s)—A novel single-blastocyst transfer algorithm reduced multiple gestation rates and improved cryopreservation rates without compromising clinical pregnancy rates in good-prognosis patients.

Keywords

ART; blastocyst; clinical pregnancy; implantation; infertility; IVF; mandatory; multiple gestation; single

Assisted reproductive technology (ART) has afforded many subfertile couples the ability to conceive. Since its inception over three decades ago, ART use has increased substantially; in 2008, there were over 140,000 cycles performed in the United States alone (1). More than 3.75 million children have been born worldwide from in vitro fertilization (IVF) since 1978 (2). With continued advancements in ART techniques and laboratory methods, pregnancy rates now are higher than ever before. However, ART is not without risks. Multiple gestation continues to be the greatest hazard of ART treatments. The maternal risks with multiple gestation include an increased incidence of gestational hypertension, preeclampsia, gestational diabetes, cesarean delivery, and maternal hospital admission (3). The neonatal risks due to multiple gestation include low birth weight, prematurity, neonatal intensive care unit admission, and increased morbidity and mortality (3).

The purpose of double-embryo transfer (DET) is to increase the likelihood of live birth, but this increased chance comes at the expense of an increased likelihood of multiple gestation and its inherent risks (4). In a meta-analysis by Gelbaya et al. (5), single-embryo transfer (SET) of cleavage-stage embryos was associated with a reduction in the probability of live birth (relative risk 0.62; 95% confidence interval, 0.53–0.72) and multiple birth (relative risk 0.06, 95% confidence interval, 0.02–0.18). In another meta-analysis, Baruffi et al. (6) evaluated studies comparing SET with DET, including cleavage-stage and blastocyst-stage embryo transfers. Once again, SET was associated with a lower live-birth rate (SET 28.4% vs. DET 42.5%, $P<.001$). Data from these meta-analyses suggest that SET results in a lower likelihood of live birth when compared with DET.

However, a recent publication has shown that in selective patient populations a SET transfer policy can maintain good pregnancy rates while reducing multiple gestations (7). Ryan et al. (8) showed that the implementation of a mandatory single-blastocyst transfer (mSBT) policy for patients at high risk of multiple gestation resulted in a 45% reduction in multiple gestations without sacrificing the programwide pregnancy rates. Simultaneously, this group also implemented patient education to improve patients' knowledge and acceptance of SET (8). As a result of this educational program, the number of patients who desired a singleton pregnancy increased from 69% to 86%.

In an effort to lower the multiple gestation rate at our institution, a mandatory single-blastocyst transfer (mSBT) policy was implemented in 2010 for good-prognosis patients. Patients were educated on the risks of multiple gestations and encouraged to accept a single-blastocyst transfer. The patients were not without choice in this matter: those who declined the recommendation underwent DET of two cleavage-stage embryos on day 3. This algorithm introduced a patient-friendly decision designed to improve the safety within our

program. We hypothesized that transfer of a single blastocyst in good-prognosis patients would result in high pregnancy rates while minimizing the risk of multiple gestation. The primary objective of this research was to determine whether the mSBT policy/algorithm reduced multiple gestation rates without sacrificing clinical pregnancy rates.

MATERIALS AND METHODS

Study Design

Institutional review board approval was obtained from by the Walter Reed Army Medical Center (WRAMC) Division of Clinical Investigation. A retrospective analysis of the Walter Reed ART database was performed, and the primary outcomes analyzed were clinical pregnancy and multiple gestation rates.

Patients

Electronic medical records were reviewed for all patients who underwent a fresh autologous ART cycle at Walter Reed Army Medical Center. The study period was defined to encompass the year before the mSBT policy was initiated (effective January 1, 2010) as well as the year following the policy. Patients from January to December 2009 comprised the “before” group, while those from January to December 2010 represented the “after” group of the mSBT policy. Study inclusion criteria applied to all patients who were <38 years old and undergoing their first fresh ART cycle in 2009 or 2010, with at least four high-grade cleavage-stage embryos on day 3 after oocyte retrieval. No donor oocyte or frozen embryo cycles were included. Demographic and IVF cycle characteristics data were recorded.

All patients received verbal and written education about the mSBT policy. Specifically, patients received brief and succinct counseling on three occasions. The mSBT policy and a review of the risks of multiple gestation were first introduced during a physician-guided group overview of the ART process (1 to 2 months before cycle start). The policy was also reiterated at cycle start, and patients were given a written copy of the policy for reference. Finally, the mSBT policy as well as the risks of multiple gestations were discussed on day 3 after oocyte retrieval. The latter counseling sessions were one-on-one with a staff or fellow physician and generally were of less than 5 minutes’ duration.

The mSBT algorithm is illustrated in Figure 1. With this algorithm, day 3 after retrieval was a decision point, and we strongly encouraged patients to proceed to a day-5 (blastocyst-stage) SET if they had 4 high-grade cleavage-stage embryos. High-grade cleavage-stage embryos were defined as either grade 1 or grade 2 based upon previously published day-3 morphologic assessments (9). Patients were extensively counseled on the maternal and fetal risks of multiple gestation pregnancies before their ART cycle, and this information was reiterated after oocyte retrieval. Patients who met the criteria were permitted to proceed to blastocyst transfer only if they agreed to transfer of a single blastocyst. If the patient desired transfer of two embryos and declined the mSBT policy, then two cleavage-stage embryos were transferred on day 3 after oocyte retrieval. All patients were asked to provide a reason for declining the transfer of a single blastocyst, and this reason was recorded.

For patients who agreed, the embryos were placed in extended culture. On day 5 after oocyte retrieval, the resulting blastocysts were evaluated by the embryologist, and a morphologic assessment was performed. Patients received a single-blastocyst transfer when there was at least one blastocyst of grade “BB” or better, based upon the grading system described by Gardner and Schoolcraft (10). If the patient did not have at least one high-grade blastocyst, the patient was given the choice to transfer one or two embryos. No patients in the group who met the initial inclusion criteria for the mSBT policy received more than a DET on either day 3 or 5 after retrieval.

With patient consent, excess blastocysts of grade “BB” or better were cryopreserved either on day 5 or day 6 (if not ready on day 5) after retrieval. No embryos were frozen at the cleavage stage. The number of patients who had at least one cryopreserved embryo was recorded.

Patient Treatment Protocol

Patients underwent either a gonadotropin-releasing hormone (GnRH) micro-dose flare or long luteal protocol, as previously described elsewhere (11). Patients were monitored with serial serum estradiol levels and transvaginal ultrasound measurements of follicle size. When there were at least two follicles ≥ 18 mm, a single intramuscular injection of human chorionic gonadotropin (hCG) was administered, and transvaginal oocyte retrieval under ultrasound guidance was performed 36 hours later. IVF or intracytoplasmic sperm injection (ICSI) was performed as indicated. Luteal support was provided with intramuscular progesterone (50 mg daily) beginning on the day of retrieval. All embryo transfers were performed with ultrasound guidance. Serum quantitative hCG testing was performed 14 and 16 days after oocyte retrieval. Transvaginal ultrasound was performed approximately 4 weeks later to confirm an intrauterine pregnancy (clinical pregnancy). The number of gestational sacs was recorded to document the number of gestations per pregnancy.

Statistical Analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (version 18, 2009; SPSS, Inc.). Student’s *t*-test was used to compare the mean values for normally distributed data. For data that were not normally distributed, a Mann-Whitney rank sum test was used to compare the mean values. Differences in outcome rates were analyzed using a chi-square test or Fisher’s exact test, as appropriate. An alpha error of 0.05 was considered statistically significant for all comparisons. All data were reported as mean $\pm$ standard deviation.

RESULTS

There were 136 patients identified from the database query who met study inclusion criteria from 2009 to 2010. There were 62 patients in 2009 who constituted the group before initiation of the mSBT policy, and 74 patients in 2010 who completed ART under the mSBT policy. The baseline characteristics of both groups are shown in Table 1.

There were no differences in mean age (30.8 vs. 31.0 years), infertility diagnosis, basal follicle-stimulating hormone (FSH) levels (6.7 vs. 6.9 mIU/mL), days of stimulation (10.8

vs. 10.9), gonadotropins per day (242.3 vs. 219.0 IU), or peak estradiol levels (4,799 vs. 5,362 pg/mL) between 2009 and 2010, respectively. The 2009 group had more oocytes retrieved per patient although both groups produced above average numbers of oocytes (19.4 [2009] vs. 16.7 [2010] oocytes, $P=.03$). The mean number of blastocysts per patient on day 5 was 2.8 (2009) versus 2.0 (2010). Consistent with the mSBT policy, the 2010 group had statistically significantly fewer blastocysts transferred per patient compared with 2009 (1.9 [2009] vs. 1.3 [2010] blastocysts, $P<.001$). All patients who opted for a transfer on day 3 after retrieval received two cleavage-stage embryos.

Pregnancy outcome, the primary end point, is summarized in Table 2. For these two groups of good-prognosis patients, the overall pregnancy rates before (77.4%) or after (74.3%) the mSBT policy were not statistically significantly different ($P=.68$). Similar findings were noted with implantation rates (54.6% vs 49.6%), clinical pregnancies (67.7% vs. 63.5%), and spontaneous abortions (6.5% vs. 6.8%) between 2009 and 2010, respectively. A statistically significant difference, however, was noted in the rate of multiple gestations between groups. Patients from 2009 had a multiple gestation rate of 43.8% compared with 14.6% after the policy was instituted in 2010 ($P=.001$). This represents a 66.7% relative decrease in multiple gestations. Finally, consistent with the fact that more blastocysts were transferred in 2009, fewer patients had 1 blastocyst cryopreserved when compared with 2010 patients (30.6% vs. 52.8%, $P=.01$).

Figure 2A depicts the dynamic change of practice and patient acceptance of day-5 SET after institution of the mSBT policy as illustrated by the blastocyst transfers over time (by quarter year). As expected, the rate of dual blastocysts transferred in the year 2009 exceeded 80% for all quarters (100% in quarters 2 and 3) with the remaining patients having a single blastocyst transferred. After mSBT began in January 2010, the ratio of SET/DET began to change. By the fourth quarter of 2010, the percentage of single blastocysts transferred was 70% compared with 30% of dual blastocysts transferred. It is interesting that the trend lines for SET and DET did not cross until the third quarter; this likely reflects a reluctance of patients to embrace and accept the change. Consistent with this finding, Figure 2B demonstrates the overall patient acceptance of the mSBT as defined by their agreement/declination of a single-blastocyst transfer. More patients agreed to a single-blastocyst transfer as the year progressed until >90% of patients in the fourth quarter chose to follow the mSBT policy. Of the patients who declined the mSBT, the majority (63.2%) desired a twin pregnancy as the optimal ART outcome, and the remaining patients declined for reasons related to travel and other logistics.

To assess the impact of the mSBT policy on our program as a whole, the pregnancy and multiple gestation rates for all patients undergoing ART at Walter Reed from 2009 to 2010 were examined. There were no differences from 2009 ($n = 384$) and 2010 ($n = 300$) with respect to overall pregnancy rates (54.9% vs. 54.0%, $P=.81$) or clinical pregnancy rates (48.3% vs. 46.1%, $P=.58$). However the multiple gestation rate for the program was statistically significantly reduced from 40.8% (2009) to 28.2% (2010) ($P=.02$), a 31% reduction.

DISCUSSION

In support of our hypothesis, the mSBT algorithm maintained high ongoing pregnancy rates and improved the number of cryopreserved embryos, while statistically significantly decreasing the number of multiple gestations. Furthermore, the mSBT algorithm not only improved outcomes in this select group of patients but for the entire ART program.

This is only the second report of an experience with mSBT in the U.S. literature. Widespread national support of a mandatory policy is not likely to exist without further confirmation of its success from independent groups. The algorithm for embryo transfer presented here may be used by other programs in the quest to minimize multiple gestation pregnancies and gain insight to patient acceptance of a mandatory policy. However, the study is limited by the retrospective design and use of a historical control group. Although the results are promising, definitive conclusions cannot be drawn without an experimental randomized controlled trial.

The impressive reduction in the multiple gestation rate in our study is similar to that reported by Ryan et al. (8), who compared IVF outcomes before and after instituting a strict mSBT policy. Their policy required mSBT in patients younger than 38 who had seven or more embryos, no prior failed IVF cycles, and at least one good-quality blastocyst (8). Implementation of this protocol resulted in a significant reduction in multiple gestation rate (41% to 15%) without a reduction in ongoing pregnancy rates (63% vs. 58%) in this good-prognosis patient population (8).

Our proposed algorithm not only supports the importance and efficacy of mSBT, but importantly it empowers the patient to be part of the decision-making process. Although our program instituted a “mandatory” single-embryo transfer policy, in fact patient choice was preserved. Patients could elect to have a DET on day 3 if they were opposed to the possibility of SET on day 5. As previously noted, there was no difference in pregnancy rates between the patients having day-3 DET and those having day-5 SET. Patient education of the results within our institution led to greater acceptance of SBT within 1 year. We feel this reflects our ongoing education of the patients as well as the success stories within our community of patients being shared among themselves.

The primary reason the patients gave for desiring two embryos transferred was not that they felt it gave them a better chance of pregnancy but that twins were their desired outcome. Education has been vital in limiting the perceived benefit of twins. It has been helpful to stress that DET may lead to triplets (which most patients do understand as undesirable) and that even SET may lead to twins (one of our SET patients is pregnant with twins).

Although our reduction in multiples (and hence increase in singletons) is highly significant both clinically and statistically, this is not a new discovery. Our colleagues in Europe have long had much stricter embryo transfer guidelines mandated and have had similar reductions in twins and greater. The manner in which pregnancies are reported (ongoing pregnancy/cycle) in the Centers for Disease Control and Prevention/Society for Society for Assisted Reproductive Technology (CDC/SART) records coupled with the pressure on private practices to compete have kept multiple rates much higher in the United States. Strict

government guidelines are not part of the clinical culture in the United States, and it may be that through efforts such as the programmatic changes described in our study that we can effectively make singleton pregnancies both the normal and expected outcome of IVF.

We devised a patient-friendly algorithm for a “mandatory” single-blastocyst transfer policy that has maintained excellent pregnancy rates and increased the number of high-quality cryopreserved embryos for the patient’s future use while greatly reducing the number of multiple gestations. The paradigm has increased safety, and it was implemented without a reduction in clinical pregnancy.

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FIGURE 1.

Summary of the mandatory single-blastocyst transfer (mSBT) algorithm from study inclusion to embryo transfer. Patients <38 years old and undergoing their first assisted reproductive technology (ART) cycle were included in the analysis (*Box 1*). On day 3 after oocyte retrieval (*Box 2*), patients with at least four high-grade embryos were encouraged to proceed to a day-5 blastocyst transfer. If the patient agreed to the mSBT policy, the embryos were placed in extended culture. If the patient declined the mSBT policy, two cleavage-stage embryos were transferred on day 3. On day 5 after oocyte retrieval (*Box 3*), patients who agreed to the mSBT had a transfer of a single high-grade blastocyst. If the blastocyst was less than “BB” grade, the patient was given the option to transfer one or two blastocysts. Csokmay. Single-blastocyst transfer algorithm. Fertil Steril 2011.

FIGURE 2.

(A) Summary of the percentage of blastocysts transferred per patient (y axis) over time per quarter year (Q1–4) from 2009 to 2010 (x axis). Transfers of a single blastocyst (*red line*) increased after the institution of the mandatory single-blastocyst transfer (mSBT) policy as marked with an arrow in January 2010. Conversely, the percentage of two blastocyst transfers (*blue line*) decreased after the mSBT policy. No patient had more than two blastocysts transferred, so the total percentage of embryos transferred each quarter equals 100%. (B) Percentage of patients accepting or declining a single-blastocyst transfer (x axis) in 2010 (quarters 1–4, y axis) as designated by their agreement or declination of the mandatory single-blastocyst (mSBT) policy. More patients agreed (*red bars*) to the mSBT as 2010 progressed and fewer patients declined (*blue bars*).

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TABLE 1

Baseline characteristics and cycle parameters between good-prognosis patients undergoing their first autologous assisted reproduction cycle before (2009) and after (2010) the institution of the mandatory single-blastocyst transfer policy.

Patient characteristics and cycle parameters	2009 (n = 62)	2010 (n = 74)	P value
Age (y)	30.8 ± 3.9	31.0 ± 4.2	.75
Diagnosis (%)			
Tubal factor	22 (35.5)	21 (28.4)	.17
Male factor	21 (33.9)	22 (29.7)	
Anovulation	9 (14.5)	20 (27.0)	
Unexplained	5 (8.1)	10 (13.5)	
Endometriosis	4 (6.4)	1 (1.4)	
PCOS	1 (1.6)	0 (0)	
Basal FSH (mIU/mL)	6.7 ± 1.7	6.9 ± 2.3	.85
Days of stimulation	10.8 ± 1.4	10.9 ± 1.7	.59
Gonadotropins per day (IU)	242.3 ± 74.9	219.0 ± 67.7	.06
Peak estradiol (pg/mL)	4,799 ± 1,721	5,362 ± 2,142	.10
Oocytes retrieved	19.4 ± 7.4	16.7 ± 7.3	.03 ^a
Total blastocysts per patient	2.8 ± 2.6	2.0 ± 2.4	.06
Blastocysts transferred per patient	1.9 ± 0.3	1.3 ± 0.5	<.001 ^a

Note: FSH = follicle-stimulating hormone; PCOS = polycystic ovary syndrome.

^aStatistically significant difference ($P < .05$).

Csokmay. Single-blastocyst transfer algorithm. Fertil Steril 2011.

TABLE 2

Pregnancy outcome data of good-prognosis patients undergoing an assisted reproduction cycle before (2009) and after (2010) the institution of the mandatory single-blastocyst transfer policy.

Outcome	2009 (n = 62)	2010 (n = 74)	P value
Pregnant (%)	48 (77.4)	55 (74.3)	.68
Implantation (%)	54.6	49.6	.44
Clinical pregnancy (%)	42 (67.7)	47 (63.5)	.61
Spontaneous abortion (%)	4 (6.5)	5 (6.8)	.94
Multiple gestation (%) ^a	21 (43.8)	8 (14.6)	.001 ^b
1 blastocyst cryopreserved (%)	19 (30.6)	39 (52.8)	.01 ^b

^aDenominator includes only those patients who were pregnant (n = 48 for 2009, n = 55 for 2010).

^bStatistically significant difference ($P < .05$).

Csokmay. Single-blastocyst transfer algorithm. *Fertil Steril* 2011.