REPRODUCTIVE ENDOCRINOLOGY AND INFERTILITY

Obstetrical and neonatal outcomes from the BEST Trial: single embryo transfer with aneuploidy screening improves outcomes after in vitro fertilization without compromising delivery rates

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OBJECTIVE: We sought to determine whether performing elective single embryo transfer (eSET) after trophectoderm biopsy and rapid aneuploidy screening results in improved obstetrical and neonatal outcomes compared with transferring 2 untested embryos.

STUDY DESIGN: The Blastocyst Euploid Selective Transfer (BEST) Trial enrolled infertile couples with a female partner up to age 42 years who were undergoing in vitro fertilization. They were randomized to receive transfer of a single euploid embryo (eSET) or to the standard of care with transfer of 2 embryos that were not biopsied for aneuploidy screening (untested 2-embryo transfer). Gestational age at delivery, birthweight, and neonatal intensive care unit (NICU) lengths of stay were compared with Mann-Whitney *U*. The risk of preterm delivery, low birthweight, and NICU admission were compared with χ^2.

RESULTS: Among the 175 randomized patients, the delivery rates were similar (69% after euploid eSET vs 72% after untested 2-embryo transfer; $P = .6$) through the fresh cycle and up to 1 frozen transfer, with a dramatic difference in multiple births (1.6% vs 47%; $P < .0001$). The risk of preterm delivery ($P = .03$), low birthweight ($P = .002$), and NICU admission ($P = .04$) were significantly higher after untested 2-embryo transfer. Babies born after untested 2-embryo transfer spent >5 times as many days in the NICU (479 vs 93 days; $P = .03$).

CONCLUSION: By enhancing embryo selection with a validated method of aneuploidy screening, a single euploid embryo with high reproductive potential can be selected for transfer. Using this approach, eSET can be performed without compromising delivery rates and improving the chance of having a healthy, term singleton delivery after in vitro fertilization.

Key words: aneuploidy screening, in vitro fertilization, preimplantation genetic screening, single embryo transfer

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Although a healthy term delivery is the ideal outcome of an in vitro fertilization (IVF) cycle,[1] nearly half of all US babies born after IVF are multiples.[2] Despite improvements with in vitro culture systems, multiple embryo transfer has remained the standard of care due to the inability to predict the reproductive potential of preimplantation embryos. When selecting embryos by the same criteria, it is mathematically impossible that transferring 1 embryo can result in an equal chance of delivery as transferring 2. However, while multiple embryo transfer improves the chance for a delivery after each IVF cycle, it carries a significant risk of multiple gestation conferring increased maternal and neonatal morbidity. Although many infertile couples initially express a desire for twins, most would prefer elective single embryo transfer (eSET) if their chance for a delivery was not compromised.[3]

To perform eSET without compromising per-transfer delivery rates it will be necessary to enhance the method of embryo selection. Having a normal complement of 46 chromosomes is a necessary, but not sufficient, requirement for an embryo to progress to a healthy newborn. Early attempts using fluorescence in situ hybridization to predict the chromosomal status of cleavage-stage embryos and preferentially transfer those predicted to be euploid were unable to improve delivery rates,[4] likely due to a negative impact of the biopsy[5] at the cleavage stage

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and poor accuracy for that technique in this clinical setting.[6] In recent years, however, use of biopsy at the blastocyst stage and more robust assays such as single nucleotide polymorphism arrays and real-time, quantitative polymerase chain reaction (qPCR) to predict the karyotype of embryos have been developed and have demonstrated high accuracy in preclinical validation,[7,8] high negative predictive value,[9] and the ability to improve delivery rates.[10] The improvement in implantation rates was of sufficient magnitude to demonstrate similar delivery rates after transfer of a single euploid embryo compared to transfer of 2 untested embryos,[11] something that had not previously been demonstrated in a randomized controlled trial (RCT).[12]

Since virtually all deliveries after eSET are singletons, we hypothesized that obstetrical and neonatal outcomes would be improved in the group randomized to euploid eSET compared with those receiving transfer of 2 untested embryos. Given the enhanced embryo selection afforded by combining embryo morphology and ploidy status, this would result in an improved chance for a term, singleton delivery.

Materials and Methods

The Blastocyst Euploid Selective Transfer (BEST) Trial was an institutional review board–approved (www.ClinicalTrials.gov registration NCT01408433), randomized, noninferiority trial comparing single embryo transfer after real-time qPCR-based comprehensive chromosome screening to transfer of 2 untested embryos. Patients with an indication for IVF who were <43 years old, with a body mass index ≤30 kg/m^2, and who had an antiMüllerian hormone level of ≥1.2 ng/mL were eligible to participate and informed consent was obtained. Patients were randomized when at least 2 embryos reached the blastocyst stage of development in a 1:1 allocation to receive either euploid eSET or untested 2-embryo transfer. In the euploid eSET group, embryos were tested with a rapid qPCR method of detecting whole-chromosome aneuploidy using assays on each chromosome and providing a result within 4 hours. Details of the rapid qPCR screening methodology have been previously described.[7]

Patients who had at least 2 expanded blastocysts with a discrete inner cell mass by day 5 were eligible for a fresh embryo transfer in the morning on day 6. Those in the euploid eSET group had their embryos biopsied in the afternoon of day 5 with qPCR analysis run overnight. Patients whose embryos were not blastocysts until day 6 or who had contraindications to a fresh transfer (risk of ovarian hyperstimulation syndrome, thin endometrium, premature progesterone elevation), had all of their embryos cryopreserved on day 6 for a future frozen transfer. Those in the euploid eSET group having a frozen transfer had their embryos biopsied on day 6 prior to cryopreservation.

The primary outcome of the study was the ongoing pregnancy rate to a viable gestation after the first embryo transfer, fresh or frozen. A summary of the results has previously been published[11] and the ongoing pregnancy rate after euploid eSET fell within the predetermined 20% noninferiority margin. Patients who received a fresh embryo transfer but did not deliver were encouraged to have a frozen transfer and remain in the group to which they were initially randomized. The current study is an analysis of the final obstetrical and neonatal delivery outcomes through hospital discharge of patients randomized in the BEST Trial after the initial fresh cycle and up to 1 frozen transfer.

Data collection

In compliance with the Centers for Disease Control and Prevention standard of practice for reporting IVF outcomes, patients were contacted after their expected date of confinement and were asked to provide demographic data such as gestational age at delivery, mode of delivery, birthweight, gender, and pregnancy complications. Institutional review board approval was obtained to perform a survey in which patients were queried in more detail about their deliveries, in particular how many days their newborns spent in the neonatal intensive care unit (NICU). Medical records were obtained and the lengths of stay and delivery outcomes were verified. Deliveries occurred at a variety of different hospital settings, both academic and community based, and comparisons between specific rare neonatal complications were not made.

Statistical analysis

Analysis was performed using the intent-to-treat principle such that patients were analyzed based on the group to which they were randomized, regardless of how many embryos were actually transferred. The risk of preterm delivery (<37 weeks), low birthweight (<2500 g), and NICU admission were compared using χ^2. The risk of very low birthweight (<1500 g), a rare outcome, was compared with the Fisher exact test. The birthweight, gestational age at delivery, and length of NICU stay were compared using Mann-Whitney *U*. A *P* value of < .05 was considered statistically significant.

Results

In all, 175 patients were randomized, 89 to the euploid eSET group and 86 to the untested 2-embryo transfer group. The 2 groups were similar in all demographic characteristics with a mean age of 35.1 ± 3.9 and 34.5 ± 4.7 years ($P = .5$), respectively. Patients in each group produced a similar number of blastocysts suitable for transfer with a mean of 5.8 ± 3.6 (range, 2–22) for euploid eSET and 5.3 ± 3.0 (range, 2–18) for untested 2-embryo transfer. In the euploid eSET group 521 blastocysts were biopsied for comprehensive chromosome screening with an aneuploidy rate of 31% (162/521). The proportion of aneuploid embryos increased with increasing age (21% for <35 years old, 34% for 35-37 years old, 56% for 38-40 years old, and 56% for 41-42 years old; $P < .001$). Two patients in the euploid eSET group did not have an embryo transfer as all of their embryos were aneuploid. After the fresh transfer, 34 patients who did not conceive had frozen embryos available and 30 have received subsequent frozen embryo transfers (17 in the euploid eSET group and 13 in the untested 2-embryo transfer group). The cumulative delivery rate after up to 1 frozen transfer was 69% (61/89) after euploid eSET and 72% (62/86) after untested 2-embryo transfer ($P = .6$) (Figure 1). In the