ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Elective single embryo transfer in women less than age 38 years reduces multiple birth rates, but not live birth rates, in United States fertility clinics

Q1 Abigail Mancuso, M.D.,[a] Sheree L. Boulet, Dr.P.H., M.P.H.,[b] Eyup Duran, M.D.,[a] Erika Munch, M.D.,[a] Dmitry M. Kissin, M.D., M.P.H.,[b] and Bradley J. Van Voorhis, M.D.[a]

[a] Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, Iowa City, Iowa; and [b] Division of Reproductive Health, Centers for Disease Control and Prevention, Atlanta, Georgia

Objective: To determine the effect of elective single ET (eSET) on live birth and multiple birth rates by a cycle-level and clinic-level analysis.
Design: Retrospective cohort study.
Setting: Not applicable.
Patient(s): Patient ages <35 and 35–37 years old.
Intervention(s): None.
Main Outcome Measure(s): Clinics were divided into groups based on eSET rate for each age group and aggregate rates of live birth per ET and multiple birth per delivery were calculated. A cycle-level analysis comparing eSET and double ET (DET) live birth and multiple birth rates was also performed, stratified based on total number (2, 3, or 4+) of embryos available, embryo stage, and patient age.
Result(s): There was a linear decrease in multiple birth rate with increasing eSET rate and no significant difference in clinic-level live birth rates for each age group. Cycle-level analysis found slightly higher live birth rates with double ET, but this was mainly observed in women aged 35–37 years or with four or more embryos available for transfer, and confirmed the marked reduction in multiple births with eSET.
Conclusion(s): Our study showed a marked and linear reduction in multiple birth rates, and important, little to no effect on clinic-level live birth rates with increasing rates of eSET supporting the growing evidence that eSET is effective in decreasing the high multiple birth rates associated with IVF and suggests that eSET should be used more frequently than is currently practiced. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Elective single embryo transfer, live birth rate, multiple birth rate, IVF

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In vitro fertilization is the single most effective treatment for infertility, and it is used with increasing frequency worldwide. In 2013, IVF treatments in the United States helped to conceive >60,000 babies, approximately 1.6% of all infants born, which is consistent with many developed countries around the world (1). Unlike many other developed countries, however, pregnancies resulting from IVF treatments in the United States are complicated by a very high rate of multiple gestations (41.1% of all IVF deliveries in 2013) (1), directly attributable to the common practice of transferring multiple embryos to the uterus to enhance pregnancy rates (PRs). During the past decade, reductions in the average number of transferred embryos have resulted in a marked decrease in high order multiple gestations (triplets and more) in the United States, but twinning rates have remained high

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Reprint requests: Abigail Mancuso, M.D., Department of Obstetrics and Gynecology, University of Iowa Carver College of Medicine, 200 Hawkins Drive, Iowa City, Iowa 52242 (E-mail: abigail-mancuso@uiowa.edu).

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due to the continued practice of transferring at least two embryos in most IVF cycles (2).

Twin pregnancies are associated with a number of short-term and long-term adverse health consequences, primarily related to the sevenfold increase in the rate of premature delivery compared to singletons (3, 4). In addition, twin gestations are costly to the healthcare system, largely due to expenses related to hospitalization and medical care of the premature infants (5). Because of these concerns, there is growing interest in reducing the incidence of twins after IVF treatments. One solution is to perform elective single ET (eSET), a practice that markedly reduces twinning rates after IVF (6–8). Some countries have adopted eSET policies, generally through legislation that requires eSET if monetary coverage for IVF procedures is provided by the government health system (9). In other countries, physicians have voluntarily embraced eSET as the standard practice for IVF, but this is often in the context of national healthcare coverage of IVF treatments (10). Compared with physicians in these countries, physicians in the United States have been slow to adopt eSET for a number of reasons; chief among them is the concern that PRs will decrease (9). With eSET, embryos not transferred to the uterus can be cryopreserved and transferred in another cycle with similar rates of pregnancy (11). However, the time and additional expenses incurred by the patient for additional cycles place a premium on high PRs in the initial cycle.

Although there is great variation in the rate of eSET among individual clinics in the United States, eSET is performed rarely nationwide, accounting for only 6% of all fresh transfers in 2010 (12). The most recent national data demonstrate somewhat higher rates of eSET, although still well below rates in many other countries (1). In the absence of a national mandate or policy, clinics voluntarily choose to emphasize eSET with their patients and do so to different degrees evidenced by differences in clinical opinion and the highly variable rates of eSET among United States IVF clinics (13). The purpose of our study was to assess eSET rates in IVF clinics throughout the United States, and to examine the relationship between eSET rates and clinic-level IVF outcomes, including live birth rates and multiple birth rates. Our hypothesis was that clinics performing higher rates of eSET would have reduced rates of multiple births, yet maintaining high PRs, as that has been the experience at our own clinic (14). To characterize the effect of eSET on individual patient outcomes, we also performed a cycle-level analysis comparing live birth and multiple birth rates for cycles using eSET versus those using double ET (DET).

MATERIALS AND METHODS

Primary IVF clinic data was collected by the Centers for Disease Control and Prevention National Assisted Reproductive Technology (ART) Surveillance System, a federally mandated reporting system that collects information regarding ART cycles (primarily IVF) performed in the United States. We analyzed the most recently available Centers for Disease Control and Prevention national data for cycles initiated during 2013, with study approval from the Institutional Review Board of the Centers for Disease Control and Prevention.

All IVF clinics reporting to the National ART Surveillance System in 2013 were included regardless of clinic size. This included 94% of all IVF clinics in the United States. The primary variable studied was the rate of eSET performed at a given clinic for all fresh autologous cycles in patient ages <35 and 35–37 years old performed in 2013. For this report we chose to focus on fresh ETs and, to avoid introducing biases from different treatments, excluded cryopreserved or "frozen" ETs and cycles using preimplantation genetic screening (PGS) or preimplantation genetic diagnosis. The primary outcomes of interest were the live birth rate per ET and the multiple birth rate per delivery. The eSET was defined as a cycle in which one embryo was transferred and at least one additional embryo was cryopreserved. This distinguishes fresh cycles in which SET was truly elective from fresh cycles in which only one embryo was available for transfer. The eSET rate was calculated as the total number of cycles that qualified as an eSET divided by the total number of ET cycles in a clinic for patients in each of the specified age groups. Live birth rate was defined as percentage of live births of at least one child (>20 weeks gestational age) divided by the total number of embryo transfer cycles in a clinic. Multiple birth rate was defined as the percentage of multiple births (twins and high order multiples) per live birth conceived by IVF in a clinic.

Clinic eSET rates were classified into the following categories for patient ages <35 years: <10%, 10%–19%, 20%–29%, 30%–39%, 40%–49%, and ≥50%. For patients in the 35- to 37-year age group, clinics were classified into the following categories: <10%, 10%–19%, 20%–29% and ≥30%. Clinics were combined into a ≥30% group for the 35- to 37-year-old age group due to the small number of clinics performing high rates of eSET in this age group. Similarly, we could not study eSET in patients aged >37 years due to the relatively small number of clinics performing high rates of eSET in this age category. We compared the average number of cycles performed at the clinics, age of patients, number of prior ART cycles, parity, racial/ethnic distribution, eSET rate, number of embryos transferred, embryo stage at transfer, proportion of intracytoplasmic sperm injection (ICSI) cycles, and implantation rate across the clinic eSET categories using generalized linear models. Models were also constructed to estimate adjusted means for clinic-level live birth rates and multiple birth rates according to clinic eSET rates. Clinic-level confounding variables assessed included clinic size (number of cycles per year), average proportion of cycles where ICSI was used, frequency of blastocyst (days 5–6) and cleavage stage (days 2–3) ET, as well as average age of patient treated, number of prior ART cycles, parity, and the racial/ethnic distribution of a clinic's patient population. Significant confounders ($P<.05$) were retained in the final models. The clinics were categorized by the eSET rate performed for the given age group, so they were not necessarily in the same eSET category for the <35 and 35- to 37-year-old age groups if they performed different rates of eSET for each group.

We then did a cycle-level analysis of all fresh, autologous ETs (excluding PGS/preimplantation genetic diagnosis cycles) to compare outcomes of eSET versus DET as previously