Not all twins are monozygotic after elective single embryo transfer: analysis of 32,600 elective single embryo transfer cycles as reported to the Society for Assisted Reproductive Technology

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Objective: To study the incidence and risk factors of multiple pregnancies after elective single ET.
Design: Historic cohort.
Setting: Not applicable.
Patient(s): Women <35 years of age undergoing elective single ET entered in the SART CORS database from 2010 to 2013.
Interventions: Not applicable.
Main Outcome Measure(s): Rate of sex discordant pregnancies. Rate of same sex pregnancies and risk factors for both same sex and sex discordant pregnancies.
Result(s): A total of 32,600 cycles were reported to SART CORS during this time period. There were 15,143 pregnancies from which 14,888 were singletons (98.3%), 23 sex discordant (0.15%) multiple pregnancies, 226 (1.5%) sex concordant multiple pregnancies, and 6 (0.01%) pregnancies without sex information. When Weinberg's differential rule was applied, the rate of dizygotic pregnancies was calculated to be 18%. Unexplained infertility was found to be the biggest risk factor for sex discordant multiple pregnancies (adjusted odds ratio 4.33, 95% confidence interval 1.4–13.1), followed by elevated body mass index (BMI). The only risk factor found for sex concordant pregnancies was undergoing a fresh transfer (adjusted odds ratio 1.4, 95% confidence interval 1.02–1.95).
Conclusion(s): Elective single ET improves, but does not completely eliminate the risk of multiple pregnancies. Patients should be counseled that there might be up to a ~2% risk of multiple pregnancies, of which up to 18% can be dizygotic. Patients with elevated BMI and unexplained fertility may be at higher risk for sex discordant multiple pregnancies and patients undergoing fresh cycles may be at higher risk for sex concordant multiple pregnancies. (Fertil Steril® 2018;109:118–22. ©2017 by American Society for Reproductive Medicine.)
Key Words: Multiple pregnancy, eSET, ART outcomes, IVF, dizygotic twins

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According to the National Center for Health Statistics, between 1980 and 2009 the rate of twin deliveries increased 76% (1). It is well known that multifetal pregnancies are associated with increased risks for mother and fetus. Maternal risks include hypertension, preeclampsia, gestational diabetes, postpartum hemorrhage among others, whereas fetal risks include prematurity, cerebral palsy, chronic lung disease, developmental delay, and, in some cases, death—with the risks increasing with each additional fetus (2–4).

The single most effective intervention used to decrease the prevalence of multifetal pregnancy resulting from assisted reproductive technology (ART) cycles has been the adoption of elective single ET (eSET) (5). Although the risk of multifetal gestation is significantly reduced with eSET, it is not completely eliminated (5–8). Certain techniques used in conjunction with eSET, specifically, intracytoplasmic sperm

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injection (ICSI), assisted hatching, and day 5 ETs, have been associated with an increased risk of monozygotic twinning (6, 7). A study by Mateizel et al. (7), analyzing factors associated with monozygotic twin pregnancies, found a 2.2% risk of monozygotic pregnancy after eSET, which was significantly reduced in frozen ET (FET) cycles compared with fresh cycles. Another study by Osianlis et al. (9) demonstrated a 2.3% risk of twin pregnancy with eSET. Of these twin pregnancies, one in five was calculated to be dizygotic twins.

The objective of this study was to determine the prevalence of and risk factors for dizygotic twin pregnancies in "stimulated" fresh and frozen cycles. The national Society for Assisted Reproductive Technology Clinic Outcome Reporting System (CORS) database was used.

MATERIALS AND METHODS

Study Design and Population

After Institutional Review Board and SART Research Committee approval, a population-based historic cohort study of 32,600 fresh and frozen autologous cycles from the SART CORS database from 2010 to 2013 was performed. Inclusion criteria were women younger than 35 years of age undergoing eSET. Patients who underwent preimplantation genetic screening or cycles without recorded outcomes were excluded. Variables analyzed included, age, race, body mass index (BMI), parity, etiology of infertility, tubal status, maximum FSH serum level, FSH dosage, pregnancy outcomes, number of babies born, number of babies live born, blastocyst transfer, assisted hatching, fresh or frozen cycle, and whether ICSI was performed. Data on birth outcomes of IVF cycles between 2010 to 2013 were collected and verified by SART and reported to the Centers for Disease Control and Prevention in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). The data in the SART CORS are validated annually with some clinics having on-site visits for chart review based on an algorithm for clinic selection. During each visit, data reported by the clinic were compared with information recorded in patients' charts. Ten of 11 data fields selected for validation were found to have discrepancy rates of $\leq$5% (10).

Outcome Measures

The primary outcome measure was the rate of sex discordant pregnancies in stimulated fresh and frozen IVF cycles undergoing eSET. Secondary outcomes included rate of same sex pregnancies and risk factors for both same sex and sex discordant pregnancies.

Weinberg's Differential Rule

Sex difference in live births was used to assess dizygosity. To establish the number of same-sex dizygotic twins, Weinberg's differential rule was used. Weinberg's differential rule uses the principle that the rate of dizygotic twinning is twice the rate of twins that are the opposite sex. As the male-to-female ratio in a population is generally 1:1, for every set of twins with opposite sex, there should be a set of same sex twins. A study by Fellman and Eriksson (11) revalidated the accuracy of Weinberg's differential rule; they found that using this rule, twinning data in Nordic countries were comparable with actual findings. Using Weinberg's differential rule, we can assume dizygosity based on difference in sex.

Statistical Analysis

Data are presented as median (interquartile range) or odds ratios (ORs) and 95% confidence intervals (CIs). Mann-Whitney *U* test was used to compare continuous data. Fisher's exact and χ^2 tests were used to compare categorical data. Logistic regression analysis was performed to identify factors that are associated with dizygotic twinning. Generalized estimating equation was used to control for repeated cycles from a single patient. Stata 12.1 was used for statistical analyses. Statistical significance was set at $P<.05$.

RESULTS

Between 2010 and 2013, a total of 32,600 fresh and frozen autologous IVF cycles in women <35 years of age undergoing eSET were recorded in SART registry and 15,143 (46.5%) live births were reported. There were 10,592 (69.9%) live births from fresh IVF cycles and 4,551 (30.1%) live births from FET cycles (Fig. 1). Singleton rate was 14,888 (98.3%) and multiple pregnancy rate (PR) was 255 (1.7%). Sex data was available in 249 (97.6%) of all multiple pregnancies. Sex concordant pregnancies were 226 (1.5%), sex discordant pregnancies were 23 (0.15%), from which there were 5 (21.7%) triplets and 18 (78.3%) twins. The rate of sex discordant twins among multiples was found to be 9%. When Weinberg's differential rule was applied, the rate of dizygotic twinning among multiple pregnancies was 18% in eSET.

Maternal and cycle characteristics from all cycles are presented in Table 1. Elective single ETs resulting in sex discordant pregnancies had a higher BMI (in kilograms per meter squared) compared with cycles resulting in singletons (OR 24.6, 95% CI 23.7–28.6 vs. OR 23.03, 95% CI 20.9–26.4; $P=.02$). Unexplained infertility was diagnosed more often in cycles resulting in sex discordant pregnancies (47.8%) than in cycles resulting in singletons (16.7%) (OR 4.33, 95% CI 1.4–13.1). Mixed infertility was diagnosed less often in cycles resulting in sex discordant pregnancies (4.4%) than in cycles resulting in singletons (21.9%) ($P=.042$). This association was lost after controlling for confounders (OR 2.6, 95% CI 0.3–22).

The eSETs resulting in sex concordant pregnancies received less total dosage of FSH (OR 1,950, 95% CI 1,424–2,775) compared with cycles resulting in singletons (OR 2,100, 95% CI 1,571–2,900), ($P=.02$). This association was lost after controlling for confounders. Cycles resulting in sex concordant pregnancies had more oocytes retrieved when compared with cycles resulting in singletons (OR 17, 95% CI 12–24 vs. OR 16, 95% CI 11–21; $P=.02$) even when controlling for confounders. Cycles resulting in sex concordant twins were more often fresh than cycles resulting in singletons, (76.7% vs. 69.8%, respectively) (OR 1.4, 95% CI 1.02–1.95).