Effect of transfer of a poor quality embryo along with a top quality embryo on the outcome during fresh and frozen in vitro fertilization cycles

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Objective: To evaluate the impact of a poor quality embryo (PQE) during double ET (DET) with a top quality embryo (TQE) on IVF outcome.
Design: A review of prospectively collected data.
Setting: Tertiary level fertility clinic.
Patient(s): All patients undergoing blastocyst transfers as part of fresh IVF (n = 939) and frozen ET (n = 1,009) cycles performed between 2010 and 2016.
Intervention(s): Single ET (SET) with TQE (group 1) was set as control and compared with outcomes for SET with PQE (group 2), DET with 2 TQEs (group 3), PQE plus TQE (group 4), and 2 PQE (group 5).
Main Outcome Measure(s): Live births and multiple births.
Result(s): The live birth rates for group 4 were statistically similar to group 1 during fresh IVF (26.5% vs. 33.7%; odds ratio [OR], 0.95; 95% confidence interval [CI] 0.53–1.7) and frozen ET (24.2% vs. 32.7%; OR, 0.75; 95% CI 0.48–1.2), although there was a trend for lower success. Conversely, multiple births were higher in group 4 for fresh IVF (19% vs. 4.7%; OR, 2.9; 95% CI 1.3–6.6) and frozen ET (10.3% vs. 2.6%; OR, 2.4; 95% CI 1.2–4.9). The live birth rates for group 2 (12.2% for fresh IVF and 14.6% for frozen ET) and group 5 (21.2% for fresh IVF and 14% for frozen ET) were lower and for group 3 were higher (40.8% for fresh IVF and 40.3% for frozen ET) when compared with group 1. Multiple births were significantly higher with DET.
Conclusion(s): This study does not support DET with one PQE along with a TQE, when there is only one TQE and one or more PQEs available for fresh IVF or frozen ET. (Fertil Steril® 2018;110:655–60. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: In vitro fertilization, single embryo transfer, double embryo transfer, multiple pregnancy, blastocyst

Single ET (SET) is the recommended approach during IVF treatment to achieve a single live birth and lower rates of multiple pregnancies when compared with double ET (DET) (2% vs. 26%–29%) (1–3). It has been increasingly adopted by many IVF units in light of guidance from the Human Fertility and Embryology Authority (4) who advocate an MP rate target of <10% with IVF. When more than one top quality embryo (TQE) at the blastocyst stage is available, SET is recommended as the live birth rate has not been found to be significantly different between SET and DET, regardless of women's age, but with a significantly lower risk of multiple pregnancy with SET (5).

Although the IVF success rate is significantly improved and triplet and higher order pregnancies reduced with improved culture systems and the move from transfer of three embryos to one or two, multiple pregnancy remains a major IVF complication (1, 6). Meta-analysis has demonstrated that multiple pregnancy carries increased morbidity compared with singleton

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pregnancies with higher rates of cerebral palsy (3.2 vs. 2.5/100), preterm labor (6% vs. <1%), and low birth weight (24% vs. 8%) (1). It has also been demonstrated that compared to two cycles of SET (to achieve a comparative live birth rate to one cycle with DET), there is no overall economic cost saving with DET, once the economic costs of managing short-term and long-term implications of multiple pregnancy have been taken into account (7).

Despite the higher rate of multiple pregnancy, DET is still generally considered by patients and professionals, especially when there are only poor quality embryos (PQEs) available, in addition to one or no TQEs on the day of transfer, in an attempt to maximize the treatment success.

Studies published that have compared outcomes in patients undergoing SET and DET are conflicting and have shown both an improvement or no benefit on pregnancy rate (PR) and live birth rate (1, 8–16). However, most studies are of small sample size, with the largest prospective studies including <250 patients (2). Furthermore, many studies have not included live birth as a primary outcome (2, 7, 9) and most of the studies have only looked at cleavage-stage ETs with only a few evaluated blastocyst transfers (8, 10, 17). What they have all consistently shown, however, is a significant increase in the multiple PR with DET (2, 7, 9, 14, 15, 17, 18).

We designed this study with the overall objective of evaluating the effect of DET with SET on IVF outcome at different grades of embryo quality. This information would be beneficial to clinicians counseling patients on the risks of multiple pregnancy against the chance of a successful pregnancy outcome. It will also hopefully aid in reducing multiple PRs without compromising live birth rates with IVF.

MATERIALS AND METHODS

Experimental Design

In this prospective observational study, we included all women undergoing their first cycle of fresh IVF/intracytoplasmic sperm injection (ICSI) (n = 939) or first frozen ET cycle (n = 1,009) between 2010 and 2016 at the ASTRA Fertility Clinic, Mississauga, Canada. All cycles were with autologous oocytes. Women with gynecological pathologies like fibroids, endometrial polyps, hydrosalpinx, and large ovarian cysts were treated before starting the treatment, but excluded if not treated before IVF. Only one cycle per participant was included. The study was approved by the institutional review board and the process of data collection was consistent with data protection regulations.

Treatment Protocols

After ovarian reserve testing, either the standard long agonist or short antagonist protocols were used for patients undergoing fresh IVF/ICSI. For patients undergoing the long agonist protocol, GnRH agonists (500 μg/d buserelin [Suprefact]; Sanofi-Aventis Canada Inc.) were started in the midluteal phase (7 days before the earliest expected menstruation) of the menstrual cycle for downregulation. Two weeks later an ultrasound was performed to confirm pituitary downregulation, defined as an endometrial thickness of <5 mm, no ovarian activity, and an E_2 level of <200 pmol/L. If downregulation was confirmed, then ovarian stimulation was started using 150–450 IU recombinant FSH (Gonal F/Puregon) or hMG (Menopur) dependant on the woman's age, ovarian reserve, and body mass index (BMI). For the antagonist protocol, ovarian stimulation was started on day 2 of the menstrual cycle by administering antagonists (Cetrorelix 0.25 mg/d; cetrotide, EMD Serono) from day 5 of ovarian stimulation.

Monitoring of the women started from the fifth or sixth day of stimulation and involved serum E_2 measurements with a series of transvaginal ultrasound scans to monitor follicular development. Human chorionic gonadotropin (Ovitrelle, 6,500 IU or Pregnyl 10,000 IU) trigger was given once three follicles were seen measuring ≥18 mm in diameter. Transvaginal oocyte retrieval was performed 36 hours later under sedation.

Depending on the results of the semen analysis, IVF or ICSI was done. When semen analysis was normal, the collected oocytes were fertilized by IVF. If semen parameters were outside of the normal parameters then ICSI was performed. For IVF, the collected oocytes were mixed with 150,000 motile sperm/mL and left overnight in an incubator. For ICSI, maturity of the oocytes was assessed after denudation. Mature oocytes with a visible polar body were injected with one mechanically immobilized sperm.

Fertilization of oocytes was assessed 18–20 hours after IVF or ICSI and was determined by the presence of two pronuclei (2PN). The embryos were subsequently cultured until day 5 or 6. Blastocysts were graded as per Gardner and Schoolcraft (19) looking at the developmental stage of the embryo (compacting stage, early blastocyst, full blastocyst, hatching blastocyst) and morphology of trophoblast and inner cell mass. The TQE were blastocysts graded as AA, AB, BA, and BB. The PQE were blastocysts graded as AC, CA, BC, CB, and CC. This study did not involve any cleavage stage transfers on day 2 or 3.

For frozen cycles, artificial hormone therapy (HT) cycles were used by starting E_2 valerate at a dose of 6 mg/d from day 1 of the natural cycle or withdrawal bleed and continued at the same dose. Endometrial thickness was checked by ultrasound scan on days 12–14 of the cycle and if the thickness was ≥7 mm, P pessaries (400 mg twice a day) were started on day 15 and blastocyst ET done on day 6 of the P pessaries.

One or two embryos were transferred after discussion with the woman. Most ETs were done with the blastocyst stage of day 5/6. A very few women had transfer on day 7. Fresh cycle ET were done on day 5 (771/939; 82.1%), day 6 (160/939; 17%), and day 7 (8/939; 0.85%). For frozen ET cycles, 383/1,009 (38%) were day 5 embryos, 583/1,009 (57.8%) were day 6, and 21/1,009 (2.1%) were day 7, 13/1,009 (1.3%) were a mixture of day 5/6 embryos and 9/1,009 (0.9%) were day 6/7 embryos.

After ET, luteal support was provided with P pessaries (uterogestan or cyclogest 400 mg) used vaginally twice per day. Women were advised to do urine pregnancy testing 14 days after ET. If the test is positive, a biochemical pregnancy was confirmed and a transvaginal scan was taken 4 weeks later. If a viable intrauterine pregnancy (IUP) was