Impact of method of endometrial preparation for frozen blastocyst transfer on pregnancy outcome: a retrospective cohort study

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Objective: To determine whether live birth rates differ by type of endometrial preparation in frozen embryo transfer (FET) cycles.
Design: Retrospective cohort study.
Setting: Academic fertility center.
Patient(s): Reproductive-aged women undergoing autologous vitrified–warmed blastocyst FETs.
Intervention(s): Comparison of two methods of endometrial preparation: programmed FET (known as group A: luteal phase GnRH agonist suppression, oral E_2, and IM P starting 5 days before ET) versus unstimulated FET (known as group B: hormone and ultrasound monitoring for follicle collapse to time transfer).
Main Outcome Measure(s): Live birth rates in group A and group B.
Result(s): Group A consisted of 923 cycles, and group B consisted of 105. When stratified by age at transfer, there was no difference in any of the measured outcomes, including live birth rates in adjusted models (adjusted odds ratio 1.0, 95% confidence interval 0.6–1.5), except in patients older than 40 years. These patients in group B had a 100% failure rate (n = 6).
Conclusion(s): In most women, unstimulated endometrial preparation with luteal support before FET has similar success compared with exogenous hormone preparation. Women older than 40 years may benefit from programmed FETs owing to the challenges of increased cycle variability expected in that age group. (Fertil Steril® 2018;110:680–6. ©2018 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: ART, endometrial preparation, frozen embryo transfers, IVF, pregnancy outcome

Frozen embryo transfers (FETs) are increasingly used in infertility practices. From 2006 to 2012, the number of FETs reported to the Society for Assisted Reproduction increased by 82.5%, whereas fresh transfers increased by only 3.1% (1). One recent Cochrane review by Glujovsky et al. (2) noted that approximately 15%–20% of all assisted reproductive technology cycles performed with a woman's own oocytes use frozen embryos. Studies have demonstrated comparable outcomes to fresh transfers, with two recent randomized controlled trials finding no significant differences in live birth rates between fresh and frozen embryo transfers in ovulatory women and women without polycystic ovary syndrome (PCOS) (3, 4). In patients with PCOS undergoing FETs, higher live birth rates and lower rates of ovarian hyperstimulation syndrome were observed (5). Frozen embryo transfers are also excellent alternatives for patients unable to complete fresh transfers, owing to logistical or medical concerns, such as an inadequate endometrial lining, inappropriate hormone levels, desire to pursue preimplantation genetic testing, and for those at risk of developing ovarian hyperstimulation syndrome (1, 6). Moreover, as national guidelines continue to endorse reducing the number of embryos

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transferred per cycle (7), more supernumerary embryos are available for cryopreservation and use in subsequent cycles. Despite their proven effectiveness and indications, the optimal protocol for endometrial preparation for FET cycles is still debated.

Two of the most commonly used endometrial preparation methods for FETs include the programmed cycle and the unstimulated cycle. In the programmed FET, ovulation is suppressed, and steroid hormonal supplementation is provided to mimic the reproductive milieu of an unstimulated cycle. In an unstimulated FET, a woman's cycle is carefully monitored to time ET according to confirmed LH surge and/or ultrasound demonstration of ovulation, followed by an endogenous luteal phase. Several studies have strived to evaluate the optimal preparation method for FETs with differing results and with many concluding that there is insufficient evidence to support one over the other (8–18). Several of these reports are limited by methodologic issues, including generalizability (such as insufficient women of advanced reproductive age) (18, 19), use of nonblastocyst embryos (14, 17, 18, 20), use of hCG trigger (21), and endpoints that do not include live birth (19, 22). To address these limitations, the objective of this study was to determine whether the method of endometrial preparation for transfer of vitrified blastocysts was associated with pregnancy and live birth rates in a large cohort.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at Penn Fertility Care in the University of Pennsylvania from January 2013 to February 2017. Women undergoing autologous blastocyst transfers were included. Those using donor oocytes, gestational carriers, or modified unstimulated cycles were excluded. Modified unstimulated cycles were defined as cycles using oral ovulation induction medications, exogenous gonadotropins, or trigger shot as part of the endometrial preparation. Patients of all ages and fertility diagnoses were included. The primary exposure was type of endometrial preparation: programmed versus unstimulated FET. Endometrial preparation type was determined at the discretion of the physician. Primary outcome assessed was live birth rates. Secondary outcomes include biochemical pregnancy, spontaneous abortion, therapeutic abortion, stillborn, and ectopic pregnancy rates.

Group A: Programmed FET Protocol

A programmed FET, defined as group A, was performed by first administering GnRH agonist suppression in the luteal phase. Ovarian suppression was confirmed after onset of menses with baseline hormonal and transvaginal ultrasound assessment. Oral E_2 was then initiated at a dose of 2 mg daily and titrated to 6 mg daily over 12 days. Transvaginal ultrasound and bloodwork was performed after 12 days of E_2, and ET was scheduled if the endometrial thickness was at least 7 mm and E_2 levels were at least 200 pg/mL. In cases of inadequate endometrial thickness or morphology or inadequate E_2 level, vaginal E_2 or higher doses of oral E_2 were administered. Intramuscular P was initiated at 50 mg when appropriate parameters were met, and blastocyst transfer was scheduled to occur on the sixth day of P supplementation. Beginning in May 2015, surveillance bloodwork was also performed on the day before transfer, and E_2 and P doses were increased if hormone levels were below the specified threshold. Transfers were cancelled for inadequate lining or inability to achieve appropriate E_2 levels before scheduling transfer.

Group B: Unstimulated FET Protocol

An unstimulated FET, defined as group B, involved patients obtaining bloodwork and then monitoring home ovulation predictor kits for LH surge. Patients with positive kit results were brought in the following day for bloodwork and ultrasound. Those with predictor kit results that were not reliable were brought in starting cycle day 12–14 for bloodwork and ultrasound and monitored for LH surge or collapse of a dominant follicle. Day 0 was defined as the day of follicle collapse. In situations in which a discrepancy was noted between home predictor kit results and ultrasound monitoring, ultrasound monitoring of follicle collapse was used to determine day 0. Vaginal P was initiated the evening of day 3, and blastocyst ET was performed on day 5. Transfers were performed under abdominal ultrasound guidance, and embryos were warmed 1 to 2 hours before the scheduled transfer.

Outcome Assessment

Serum hCG was measured 10–12 days after ET. Human chorionic gonadotropin measurements greater than 1 ng/dL were considered positive and repeated according to the clinic protocol. Biochemical pregnancy was defined by a positive hCG that spontaneously dropped to <1 ng/dL and in the absence of an intrauterine gestational sac. A clinical intrauterine pregnancy was defined as the presence of an intrauterine gestational and yolk sacs on transvaginal ultrasound. A spontaneous abortion was defined as loss of a clinical intrauterine pregnancy, whereas a therapeutic abortion was an induced loss of a clinical intrauterine pregnancy. Pregnancy losses at greater than 20 weeks' gestation were defined as stillbirths.

Analysis

To have an 80% power to detect a 15% difference in live birth rates, favoring group A, it was calculated that 412 cycles in group A and 103 cycles in group B would be necessary. Multivariable logistic regression was performed with determination of confounders with backward elimination, as well as a priori variables that were determined to be of clinical significance. Variables fit in the model include age at retrieval, body mass index (BMI), infertility diagnosis, preimplantation genetic testing (PGS/PGD), year of transfer, and number of embryos transferred per cycle. Overall pregnancy, biochemical pregnancy, spontaneous abortion, therapeutic abortion, stillborn, ectopic pregnancy, and live birth rates in group A were compared with those in group B.

Analysis was performed using STATA version 14 (StataCorp). Approval for the study was obtained from the University of Pennsylvania's institutional review board (protocol 827237).