Programmed versus natural frozen embryo transfer: which is the best nest?

For implantation to occur, the endometrium needs to be in a receptive state that closely matches the developmental stage of the embryo. Coordinating the transfer of a frozen embryo is key given the ideal window of implantation (WOI) in the mid-secretory phase is short. The time of maximum uterine receptivity is from post-ovulatory days 6-10 (cycle days 22-24 of an idealized 28-day cycle). During this phase, stromal cells undergo pseudo-decidualization and an epithelial cell-like appearance due to the accumulation of glycogen and lipid droplets. These epithelial cells begin to secrete cytokines and growth factors while developing pinopodes and cell adhesion molecules to prepare for invasion of the trophoblast. Without implantation, the endometrium enters the late secretory stage and prepares for menstruation.

In a natural conception, the maturing oocyte within the follicle coordinates the ideal time of blastocyst apposition to the endometrium. Rising estrogen stimulates endometrial proliferation and induces progesterone receptors. In an in vitro fertilization cycle, the supra-physiologic rise in estrogen and early secretion of progesterone with human chorionic gonadotropin (hCG) trigger may shift the WOI 16-24 hours earlier compared to a natural conception. This may be behind why some anovulatory women, who have higher peak estradiol levels and are more prone to premature progesterone secretion, have better pregnancy rates in frozen embryo transfer (FET) cycles compared to fresh transfers. In contrast, ovulatory women have comparable pregnancy rates in fresh and frozen transfers (1, 2).

Two recent advances in our field, vitrification and preimplantation genetic testing, have catapulted the rates of FET cycles in the past 5 years. The number of clinics performing freeze-all cycles gained traction as preliminary data from vitrification showed improved survival rates compared to slow freeze and comparable pregnancy rates in ovulatory women to fresh transfers. Notwithstanding the debated topic of whether it should be universally applied, the rates of preimplantation genetic testing for aneuploidies (PGT-A) have also substantially risen, and these two trends have increased the number of FET cycles in current practice. However, the proportion of PGT-A tested and presumed euploid embryos failing to implant is approximately 40%, highlighting the need to continue focus on the ideal endometrial timing and hormonal preparation. Furthermore, with a 10% to 15% biochemical/miscarriage rate after euploid embryo transfers, the very fate we try to avoid when employing PGT-A, other areas such as the impact of biopsy of a less populated trophectoderm and synchrony of embryo to endometrium need further evaluation.

Using microarray molecular analysis, Simon has confirmed the pioneering work of Rock and Noyes showing approximately 25% of women have a delayed endometrial development. Their work in recurrent implantation failure suggests for some of these women, a delay in transfer beyond the typical progesterone exposure may be beneficial on a case-by-case basis. However, the human embryo has proven itself to be more patient than the endometrium, and the degree of delay detected by ERA would have to exceed the ability of the embryo to survive in utero awaiting the WOI.

For the clinician, there are two main options for a frozen transfer. Programmed FET cycles use estrogen to proliferate the endometrium and progesterone to create secretory changes and suppresses natural ovulation using either a gonadotropin-releasing hormone (GnRH) agonist or antagonist. Benefits of the programmed cycle are less monitoring for patients and ease of scheduling transfers. For programmed cycles without a GnRH agonist, the frequency of monitoring increases to detect whether a GnRH antagonist should be added. For ovulatory women, a hormone-free option is often preferred. This requires frequent monitoring of urine or serum luteinizing hormone levels beginning on the tenth day of a 28-day cycle until the precise detection of the luteinizing hormone surge is determined. Ultrasound monitoring of the developing follicle and uterine lining measurements also ensure an ideal transfer month. Cycle cancellation rates are higher with this method if a clear surge is not detected. Modified natural cycles involve ultrasound monitoring of the developing follicle followed by hCG administration when the follicle reaches $\geq$17 mm with an estradiol level above 200 pg/mL. This reduces both cancellation rates and shortens the duration of monitoring, as well as improving corpus luteum function.

In this issue of *Fertility and Sterility*, Alur-Gupta et al. (3) conducted a retrospective study examining the effect of natural versus programmed endometrial preparation in FET cycles on live birth rates. While this is not a prospective study, they sought to address this critical topic: evaluating the degree to which natural ovulation or hormonal preparation impacts the receptive window of the endometrium. The study built on past research comparing these two modalities. A Cochrane review found four previous randomized control trials but insufficient evidence to recommend one modality over another (4). Alur-Gupta and colleagues (3) included a total of 1,028 FET cycles using vitrified blastocysts (923 programmed cycles and 105 natural cycles). Primary endpoint was live-birth rates, and secondary endpoints were biochemical pregnancy, spontaneous abortion, therapeutic abortion, stillborn and ectopic pregnancy rates, and the study was adequately powered. The authors did not find differences in live-birth rates comparing programmed or natural FET cycles, and similar live birth rates persisted when restricted analysis was performed, considering only PGT-A cases and freeze-only cycles.

Strengths of this study are the large number of cycles, and outcomes were adjusted for potential confounders such as anovulatory cycles, diminished ovarian reserve and number of embryos transferred. They also included a modern-day variation of reasons for FET, the majority of which were extra embryos (47-51%), logistical reasons (27-29%), and elevated progesterone levels during the fresh cycle (4-9%).

Although the lack of exclusion criteria allowed for a high number of included cycles, the heterogeneity of included

cycles reduced the applicability of the study findings. With only six women over 40 years of age in the unstimulated FET group, and only one of six with euploid embryos, there were insufficient data to assume women over 40 years-old are not good candidates for natural FET cycles. For women over 40 years-old who prefer a non-medicated cycle, a modified natural cycle may be a good alternative. The function of the corpus luteum should improve after hCG, and ovulation induction agents used to improve corpus luteum function are often better tolerated than IM progesterone. The findings for women over 40 years of age make sense, in that older women have slower blastulation rates, thus a higher proportion of their embryos blastulate on days 6-7. Implantation rates of these embryos in fresh transfers are reduced by 15% to 18% but are restored in a programmed cycle, suggesting women who blastulate late may fall into the tail end of the WOI with consequent reduced implantation rates. Indeed, Wilcox demonstrated that women who implant beyond the normal window of implantation have a higher incidence of pregnancy loss (5).

Ultimately, between the embryo and endometrium, the embryo has proven itself to be the more adaptable of the two, provided it is placed within a secretory environment at the ideal or earlier stage within a receptive endometrium. Molecular diagnosis of endometrial receptivity based on its transcriptomic signature shows promise for a small subset of patients with recurrent implantation failure, but findings are yet to be independently verified. Although the debate over the ideal progesterone replacement regimen in medicated FET cycles will continue, when considering natural verses programmed cycles, it appears that both methods yield comparable live birth rates.

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