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COMMENTARY

Frozen-thawed embryo transfers: time to adopt a more "natural" approach?

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Abstract

The increasing use of frozen–thawed embryo transfer (FET) cycles has magnified the focus on endometrial preparation protocols in assisted reproduction. Emerging evidence suggests that natural cycle (NC) FETs are associated with improved outcomes, and that providers should consider increasing the utilization of NC FET at the expense of the currently favored artificial cycle (AC) FET as primary method for endometrial preparation.

Keywords In-vitro fertilization (IVF) · Assisted reproductive technology (ART) · Frozen-thawed embryo transfer (FET) · Natural frozen-thawed embryo transfer

Many advances have been made in the area of assisted reproductive technologies (ART) over the last 40 years. Ultimately, the cumulative success of these advancements comes down to the interaction of a competent embryo and a receptive uterine endometrium during the optimal window of implantation. Improvements in cryopreservation techniques have allowed for the segmentalization of the in vitro fertilization (IVF) process into controlled ovarian hyperstimulation (COH) with cryopreservation of either oocytes or embryos ("freeze-only"), followed by embryo transfer as a separate step. Major reasons for the increased use of this freeze-only strategies include, but are not limited to, increased use of pre-implantation genetic testing to screen for aneuploidy (PGT-A), risk reduction for those at high risk of ovarian hyperstimulation syndrome (OHSS), premature progesterone elevation on the day of oocyte maturation trigger, intra-cycle discovery of structural abnormalities of the uterus or fallopian tubes, and random start ovarian stimulation, commonly done for fertility preservation in newly diagnosed cancer patients [1–4].

Adverse maternal and neonatal pregnancy outcomes have been noted with frozen embryo transfer cycles (FET) [5]. Evaluating pregnancy and birth outcome differences between different FET endometrial preparation protocols is an area frequently studied via retrospective data [1].

In this month's issue of JARG, Wu et al. report the findings of a systematic review and network meta-analysis regarding endometrial preparation protocols for frozen–thawed embryo transfer cycles, based on data from 26 randomized controlled trials (RCTs) and 113 cohort studies [6]. They found that programmed cycles/artificial cycles (AC) were associated with lower live birth rates when compared with other endometrial preparation protocols, including true natural cycles (tNC) and modified natural cycles (mNC), in which ovulation was triggered using injectable human chorionic gonadotropin (hCG). Women who conceived following a programmed FET were at an increased risk of pregnancy-induced hypertension, postpartum hemorrhage, and very preterm birth compared with those who conceived following tNC FET.

The number of ART cycles has increased globally over the last decade, with over 1,200,000 cycles performed in the USA and Europe combined in 2016 [7, 8]. The use of frozen embryo transfer has seen a drastic increase during this time, with some estimates suggesting a tripling in women over 40 in the USA between 1996 and 2013 [9]. Despite this increase in

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utilization, recent data suggest increasing rates of maternal hypertensive disorders of pregnancy (mHTN) and infants born large for gestational age (LGA) following frozen embryo transfer [5]. A recent review from our group explored the possible pathological rationale for these findings, with perhaps the most compelling evidence suggesting the loss of the corpus luteum in programmed frozen embryo transfer cycles as the leading cause of the association between FET and LGA/mHTN disorders [10].

Frozen embryo transfers are performed 3 to 5 days post-ovulation during the natural menstrual cycle (deemed a natural transfer), or with a programmed menstrual cycle using exogenous estradiol and progesterone supplementation. Programmed FET cycles are especially useful for patients with irregular menses, but are used in all patient types given the ease of scheduling of transfers juxtaposed with the possible unpredictable nature of scheduling natural cycle FETs. A study by Alur-Gupta et al. demonstrated similar live birth rates after either programmed or natural FET cycles [11]. However, only 10% of the 1028 transfers in this study were done with a natural cycle preparation. A recent retrospective study from Sweden investigated differences in obstetrical outcomes with programmed cycles without a corpus luteum, compared to natural or modified FET cycles [12]. Natural cycles represented over 60% of all cycles evaluated and results demonstrated programmed FET cycles were associated with increased rates of mHTN, cesarean section, postpartum hemorrhage, post-term birth, and macrosomia when compared to natural or modified FET. The difference in postpartum hemorrhage (PPH) was particularly striking, with 19.4% of patients in the programmed cycles experiencing PPH compared to 7.9% in the natural cycle cohort [12]. Similarly, a study by Makhijani et al. demonstrated a twofold increase in mHTN in programmed cycles compared to natural cycles, and concluded that natural cycle FET should be the first-line option given to patients undergoing FET [13]. Finally, a study by Zhang et al. demonstrated that the use of letrozole, and in some cases gonadotropins, in abnormally cycling polycystic ovary syndrome patients had a decreased incidence of hypertensive diseases in pregnancy compared to patients with a programmed cycle, further demonstrating the need for corpus luteum development [14]. This study also demonstrates that all patient subtypes can benefit from non-artificial frozen embryo transfers, making this a viable option across infertility clinics.

What is the underlying molecular mechanism for the differences observed? As reviewed by Singh et al., the absence of a corpus luteum in early pregnancy in programmed cycles is associated with a lack of vasoactive compounds which may increase the risk of pre-eclampsia. Specifically, the absence of circulating relaxin and vascular endothelial growth factor in early pregnancy potentially contributes to abnormal placentation during programmed FET cycles, which may represent the cause for increased obstetrical complications observed after these cycles [15].

The true prevalence of programmed FET cycle use in the USA is unclear from published data, but it appears that use of natural FET cycles is currently similar to the data presented by Alur-Gupta et al. (less than 10%) [11]. That may explain the relative paucity of studies in this area from the US ART programs. While research to date does not demonstrate a definitive relationship between programmed FET and mHTN, the literature seems to present a strong enough cause for our community to rethink the high use of programmed FET cycles. There is certainly a need for more high-quality research, particularly with more well-designed randomized controlled trials, to substantiate these findings before completely abandoning the programmed cycle. Even so, given the possible decrease in mHTN pregnancy complications, it would seem beneficial for infertility clinics across the USA and internationally to strongly consider using natural FET cycles over programmed cycles whenever possible.

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