Freeze-only in vitro fertilization cycles for all?

In recent years, infertility treatment specialists are increasingly recommending the freezing of all available good quality embryos and are scheduling patients for delayed embryo transfer during more controlled and endocrinologically more physiologic (natural or hormonally programmed) cycles. This is a reasonable, in fact necessary, approach in patients at risk for developing ovarian hyperstimulation syndrome (OHSS) or undergoing preimplantation genetic testing cycles. However, the wider, universal use of freeze-only cycles for all patients undergoing in vitro fertilization (IVF) is still in question. What is the evidence that such an approach leads to improved live-birth rates and to better perinatal outcomes? Are there risks accompanying delayed transfer of previously frozen human embryos? Is there experimental evidence indicating the physiologic underpinnings and thus provide the biologic basis for such an approach? Are there lingering questions in need for answers before a freeze-only approach is universally adopted?

The data on ongoing pregnancy rates provided by Shapiro and colleagues brought to the forefront this important issue (for review, see ref. 1) (1). In 2011, these authors hinted at the biologic basis explaining the improvement in pregnancy rates following the transfer of previously frozen embryos by suggesting that it is a dysynchrony between embryonic age and endometrial maturation (development of the window of implantation) which potentially provides the pathophysiologic explanation of some of the clinical observations (see #12 in ref. 1)(1). In their 2013 article (see #11 in ref. 1) (1), results on the ongoing pregnancy rate following day 6 frozen blastocysts transferred on the equivalent of day 5 endometrium (54.3%) showing similar results to day 5 fresh embryo transfers (56.5%) further support this suggestion and put in question the conclusion that fresh transfers are potentially always worse than frozen transfer results. Considering that the prior Shapiro publications involved both day 5 and day 6 fresh blastocyst transfers, the statistically significant results reported may be explained by the inclusion of day 6 blastocysts in the fresh transfers, thus contributing to the overall lowering of the ongoing pregnancy rate observed in the fresh transfer group. So, one could conclude that it is not the frozen versus the fresh embryo transfer driving the results, but it is the timing of transfer vis a vis endometrial maturation and the establishment, in cellular and molecular terms, of the window of implantation that explains the clinical observations.

The incidence of adverse perinatal outcomes (preterm birth, small for gestational age, low birth weight, perinatal mortality) and other complications (antepartum hemorrhage) following fresh versus frozen and delayed embryo transfer have also added support for a freeze-only approach. Multiple non-randomized clinical studies and a META-analysis (2) show a reduction in such adverse perinatal outcomes following frozen embryo transfer cycles. However, data on pre-eclampsia are less clear and development of large for gestational age babies (an adverse perinatal outcome similar to the well-known large offspring syndrome described in the domestic animal literature) appear to be increased following frozen embryo transfer regardless of whether the freezing protocol involved slow freeze or vitrification (3). Therefore, one can conclude that aspects of the periconceptional milieu may contribute to normal or abnormal implantation and placentation, thus leading to varying degrees of severity with respect to establishment of pregnancy, growth of the fetus, and other perinatal complications.

In their totality, the data to date do not support a shift to freeze-only cycles for all. If anything, the data point toward a selective application of this approach. Can we identify the patients at risk and therefore recommend freeze-only cycles to them or are we forced to apply this standard to all?

The Wang et al. (4) article in this issue of *Fertility and Sterility*, attempts to shed further light to the debate of fresh versus frozen embryo transfer. First, it is important to recognize the authors for agreeing to change the terminology in their article from freeze-all to freeze-only. The term freeze-all implies freezing of all the embryos, a fact that does not reflect practice and potentially misleads patients who may have had a certain number of eggs fertilized, but only a fraction of these zygotes frozen either at the cleavage or the blastocyst stages. The term freeze only should be universally adopted to label those cycles during which no fresh embryo transfer is planned or performed. Second, in this matched cohort, multicenter, retrospective study, the authors provide evidence as to which patients may benefit from a freeze-only approach. Even though the authors' conclusion is that freeze-only cycles are associated with significantly higher pregnancy and implantation rates, the actual results do not support justification for a change in practice for all patients, as implied in the manuscript. Attention to the stratified analysis shows that it is the progesterone level that drove the results and not necessarily the fresh versus frozen approach. A role for progesterone in creating a dysynchrony between embryonic and endometrial development has been previously suggested. The data from the present multicenter study, make this hypothesis more compelling and credible as it suggests a cellular/molecular mechanism potentially explaining the clinical observation. In addition, age appears to also play a role, as there was a trend for older patients benefiting from a freeze-only approach. This needs further investigation.

To date, only one randomized controlled clinical trial evaluating live births in fresh versus freeze-only IVF cycles has been published (5). This study showed a statistically significant 7.3% absolute increase in live births following delayed, frozen embryo transfer in polycystic ovary syndrome (PCOS) patients. Of great interest in that report was this increase in liveborns was due to an increase in pregnancy loss among biochemical pregnancies (32.7% vs. 22%) and an overall pregnancy loss (25% vs. 14.6%) and second trimester pregnancy loss (11.9% vs. 5%) among clinical pregnancies in the fresh transfer group. These observations suggest the mechanism(s) for these miscarriages may involve the process of placentation as well as potential effects of aspects of PCOS on the endometrium or on the maternal response to pregnancy. In that study, there were no differences in progesterone (mean ± SD: 1.0±0.6 vs. 1.0±0.5 ng/ml) or estradiol (mean ± SD:

4,141±2,159 vs. 4,288±2,210 pg/ml) levels between the two groups on the day of human chorionic gonadotropin trigger, indicating that other factors related to PCOS may have contributed to the results.

As of August 2017 and based on current evidence, it is reasonable to recommend a freeze-only approach for patients at risk for developing OHSS; patients whose embryos are undergoing trophectoderm biopsy for genetic testing; patients with PCOS; and patients with premature elevation of serum progesterone. However, what defines elevated progesterone remains to be determined as there are variabilities between assays and between centers and thus a conclusion from one program or from one laboratory may not be applicable to another. In addition, recent publications suggest that an elevated estradiol may contribute to adverse perinatal outcomes. Should a direct or indirect role of an elevated estradiol be further investigated in deciding whether a freeze only cycle should be recommended?

Finally, there are a number of additional questions to be considered: do older patients stand to benefit from a freeze-only approach as suggested, but not proven, by Wang et al. (4)? Is there a difference between cleavage stage (day 3) and blastocyst stage (day 5) transfer results between fresh versus frozen embryos? Even though vitrification appears to be dominating the practice of freezing of human embryos, are there differences in the results following slow frozen versus vitrified human embryos?

In the dawn of the era of precision (personalized) medicine, it appears that we should stop following a one size fits all approach. We should consider defining parameters to discriminate and choose the optimal approach for each of our patients. The Wang et al. (4) article in this issue of *Fertility and Sterility* indicates elevated progesterone as the driving force behind the decreased implantation and ongoing pregnancy rates following transfer of fresh embryos. However, further studies to define the threshold level(s) of progesterone are needed. Even though the biologic basis of a premature exposure of the endometrium to an elevated progesterone and shift of the window of implantation can be hypothesized as the cellular mechanism explaining the clinical observation, the exact progesterone levels and timing of such elevation need further definition and possibly evaluation by each clinical program's review of their own results. Similar considerations for elevated estradiol levels should also be explored as the mechanism by which an elevated estradiol affects implantation and placentation is not clear at the present time. In conclusion, it is clear that some subgroups of patients would greatly benefit from a freeze-only approach and we should all be encouraged to recommend it. The increased cost and emotional toll of a delayed transfer should not deter us from making the case for avoiding a transfer during the fresh cycle in these subgroups of patients. However, applying this approach to ALL patients may be considered premature at the present time and should await publication of two very large, randomized clinical trials evaluating the results of a freeze-only approach in non-PCOS patients (NCT02471573 and NCT03118141).

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