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COMMENTARY

Time to "cool off"? Examining indications for "elective deferred frozen embryo transfer"

Alexander M Quaas[1] · **Karl R Hansen**[1]

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The first birth from in vitro fertilization (IVF) in 1978 occurred for the indication of tubal factor infertility [1, 2]. The goal was to unite the male and female gametes outside the body and transfer the resulting embryo into the uterus to bypass the obstruction that prevented fertilization and implantation. Since that time, the indications for the use of assisted reproductive technology (ART) including IVF have expanded to include virtually all causes of infertility as well as non-infertility indications such as preimplantation genetic diagnosis for the prevention of genetic disease. Over the past decades, the IVF process has evolved through improvements in stimulation protocols and laboratory techniques.

Often, adaptation of new technologies occurred prior to, in parallel with, or in the absence of rigorous scientific evidence to support effectiveness and safety. Advances in the field of ART seldom (arguably never) occur in isolation and temporally separated. The last decade in the evolution of our field has witnessed a dramatic expansion in technologies of cryopreservation, genetic analysis, and non-invasive embryo assessment.

In the early days of ART, providers sought to overcome low implantation rates with the transfer of multiple embryos, under the assumption that success rates of frozen embryo transfers (FETs) would be lower, especially prior to the advent of vitrification. However, as embryo cryopreservation became more commonplace, observational studies started to suggest that the perinatal outcomes of FETs compared to fresh transfers were "similar or even better, particularly regarding fetal growth" [3] [4]. Pregnancy and live births rates with FETs were approaching those of fresh cycles, likely through increasing use of vitrification [5].

These developments gave rise to the concept of universal cryopreservation of entire embryo cohorts in lieu of fresh transfer [6].

In this issue, Basile and Garcia-Velasco examine the topic of "frozen fever" in their review article [7]. Specifically, they pose the question as to when the "elective deferred embryo transfer" concept should be used, which involves segmentation of treatment via cryopreservation of oocytes or embryos and subsequent frozen embryo transfer (FET). For specific indications? Universally? Does segmentation of treatment "improve the soil" or "harm the seed"?

In order to provide the background to this question, the authors review the relevant laboratory and clinical developments that led the field of ART to this point. A succinct history of embryo and oocyte cryopreservation, including the move from "slow-freezing" techniques towards vitrification, is followed by an overview of recent trends in stimulation protocols, with the goal of ovarian hyperstimulation syndrome (OHSS)–free clinics. The advent and increasing use of preimplantation genetic screening (PGS) is mentioned prior to a review of the literature on perinatal and obstetric outcomes with cryopreserved versus fresh embryo transfers.

The evidence for the central question "Who benefits from a freeze-all strategy?" is then presented. The authors agree that a freeze-all approach is useful for specific indications, such as the prevention of OHSS in high responders and the timely indication of reduction in Zika-related morbidity in affected areas (Table 2, [8]).

However, when it comes to a universal freeze-all strategy, the authors are more cautious. A recent meta-analysis, which

Capsule Advances in cryopreservation techniques and scientific evidence demonstrating benefits of frozen embryo transfers have led to an increased use of a "freeze-all" strategy in ART. This commentary examines this trend and introduces the review article by Basile and Garcia-Velasco on the topic.

✉ Alexander M Quaas
Alexander-Quaas@ouhsc.edu

[1] Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, 800 Stanton L. Young Blvd., Suite 2400, Oklahoma City, OK 73104, USA

is central to this debate, is critically reviewed [9]. The reader is cautioned to await further evidence prior to adapting a universal "freeze-all" strategy, especially in the face of laboratory variations in vitrification expertise. Where will we obtain this additional information?

The authors mention that an ongoing randomized controlled trial from the UK (the "E-FREEZE" trial) may help answer this question. A very recent prospective multicenter trial comparing fresh versus frozen embryos in patients with polycystic ovarian syndrome [8] demonstrated that FETs were associated with an increased rate of live birth, decreased rates of pregnancy loss, and ovarian hyperstimulation syndrome, but an increased rate of pre-eclampsia, as well as a statistically non-significant trend towards a higher rate of neonatal deaths ($p = 0.06$). However, this study was conducted in a specific patient population and transfers were performed at the cleavage stage in both arms, limiting our ability to generalize the results to the broader population of patients undergoing IVF wherein blastocyst cryopreservation and transfer are more common.

Given that prior studies on this topic are heterogenous [4], with few high-quality randomized trials [10], investigators have advocated prospective trials in the general infertility population, including patients with and without currently common IVF practices such as blastocyst culture and preimplantation genetic screening (PGS) [11]. Indications for PGS are evolving, and the benefits and harms of blastocyst versus cleavage-stage transfer are a matter of ongoing research and debate [12, 13]. It is currently unclear whether a possible future multicenter "fresh versus frozen" ET trial should include patients with cleavage versus blastocyst transfers, with and without the use of PGS, normal or poor ovarian reserve, as well as different types of stimulation and laboratory protocols [10]. Plans regarding the choice of primary outcome, data analysis plan, and adverse outcome collection also remain to be determined.

Additional reflections regarding the design of a possible future multi-center trial on new strategies for embryo transfers, including fresh versus frozen, were recently published by Cedars [14]. Her proposal advocates for the concomitant analysis of "two interventions that build on each other," freeze-all with and without PGS, compared with fresh transfer without PGS—with a primary outcome of time to live birth.

The results of such a trial may influence whether the "frozen fever" in ART will persist. Until then, Basile and Garcia-Velasco recommend we "cool off" and wait for additional data.

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