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EDITOR'S COMMENTARY

The dawning of a new ice age for human oocyte cryopreservation

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While global alterations in temperature "raise" the level of discourse concerning human choices and the future of species currently occupying the planet, so too has the level of discourse risen lately regarding the subject of human oocyte cryopreservation and the treatment of human infertility. As mentioned last month, extensive coverage of this topic was in evidence at the most recent ASRM meeting. And the debate regarding removal of the "experimental" label appears poised to effectively recognize this ART as one of practical value to both clinicians and their patients.

Many factors enter into the uses of cryopreservation technology and with the surging front of fertility preservation bolstering the need to achieve higher levels of success for storage of gametes, embryos, and tissues, it is an appropriate time to gauge the past, present and future prospects of a field that extends well beyond the original purview of infertility management.

Several questions beg addressing. What methods are the most safe and efficient? As discussed below, queries into the benefits or disadvantages of slow freezing compared to vitrification continue and the present issue of JARG (as with those of the recent past) underlines a spectrum a technicalities awaiting resolution that are not commonly evidenced (or popular) in public presentations. How do patient specific factors enter the choice of treatment and utilization of one technique over another? And what level of confidence do we have that the introduction of one or many cryopreservation protocols into the daily routine of the IVF laboratory has been "ergonomically" matched with case load, embryologist training, and the long term performance of centers with widely varying numbers of patients seeking a range of treatment options?

While answers to these and other questions await the emergence of data sets derived from traditional (live births and follow-ups) and highly touted "omics" (for proximate oocyte and embryo quality evaluation) assessments, we think it helpful to consider such matters at the dawning of this new age for oocyte cryopreservation in human ARTs.

To this observer, the sometimes contentious and exaggerated claim that one method is better than another has assumed the character of the trivialized. The basis for such comparisons for cryopreserved mature oocytes, as noted by Gook and Edgar in this issue, center on statements suggesting that only vitrification can achieve clinical outcomes (implantation rates and live births) comparable to those obtained with fresh oocytes. These leaders in the field now demonstrate in JARG that slow freeze protocols indeed approach successful outcome measures with fresh oocytes when patient age is taken into consideration (using a cutoff of 38 years old). This should come as no surprise to students of oocyte aging given the gradual loss of physiological regulators known to attend the chronic storage of ovarian oocytes with advancing maternal age. The real question becomes not one of choosing the correct technique but one of implementing best practice guidelines that no doubt reflect age as well as other patient specific parameters such as stimulation regimes and laboratory conditions. In this sense it is useful to recall recommendations that arose from the first International Congress on Fertility Preservation held in Brussels late in 2009.

Charged with the task of summarizing several days of intense debate over the most proper approaches to ovarian tissue cryopreservation, Professor Roger Gosden noted that

Capsule Recent breakthroughs in human oocyte cryopreservation both set the stage for adoption of this technique in certain clinical situations and at the same time urge that caution be exercised since many technicalities have yet to be resolved for widespread implementaion in IVF clinics.

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both vitrification and slow freeze technologies are appropriate and effective strategies to achieve the end of viable tissue following thawing. He urged the audience to remember that practical issues should trump the comparisons of the equivalent techniques of slow freezing and vitirification. Thus, if a laboratory has already purchased and established slow freeze technology then they should proceed with this approach. However, for laboratories not in possession of a slow freezed apparatus, then vitrifcation offers a less expensive and just as effective solution for the establishment of ovarian tissue cryopreservation. In both cases, the matter at hand is not which approach to use but instead offering patients a safe and efficient way to store either oocytes or ovarian tissues with acceptable and standardized protocols.

Perhaps a more telling line of enquiry should ask whether the daily practice of oocyte cryopreservation has withstood the test of time with respect to protocol standardization? With either slow freeze or vitrification, the normalization of protocol has yet to achieve something even remotely reproducible. Visits to IVF clinics around the world over the past 5 years reinforces suspicions regarding the absence of uniformity and variability in protocols. From cryoprotectant combinations and devices to the timing of re-equilibration and solution composition, there is little consensus as to best practice protocols that would from center to center evoke a sense of commonality. A good case in point is the matter of patient age alluded to above. Another case in point has to do with the time that is typically allotted either prior to cooling or following thawing. Certainly, case load alone and number of available skilled staff are both rate limiting in effecting a daily schedule that is expected to meet the overlapping patient needs from morning to afternoon or under the context of weekend schedules. How long are freshly retrieved oocytes "resting" while their appointed "chill" approaches? And even more illustrative is the case where subsequent to thawing, who keeps track of the biological clock before inseminating and how long should you wait before performing ICSI or IVF(less likely)?

With respect to recovery time before ICSI, there seems to be consensus that in centers deploying slow freeze technology, the magic time interval is 3 h from thawing to the time of ICSI. When queried about the origins of this practice, most embryologists confide that a "POL SCOPE paper" some years ago designated this as the time required for spindle reassembly. Matters seem to be a bit more urgent with warmed vitrified oocytes since high cryoprotectant concentrations are known to have strong stabilizing effects on the meiotic spindle. In this case, perhaps an hour is sufficient. But what happens if you put yourself into the cytoplasm of a human oocyte and ask when would be the best time to do ICSI if your objective is production of a genetically stable zygote? To my knowledge, there is but one paper that has attempted to answer this question.

The Tecnobios Procreazione group led by Borini and colleagues in Bologna performed such a study that was published in Human Reproduction in 2009 (see Bromfield et al., Meiotic spindle dynamics in human oocytes following slow-cooling cryopreservation. Hum Reprod. 2009 24 (9):2114–23, Pub Med PMID: 19465461). Two observations gleaned from these studies deserve attention. First, spindle recovery was maximal by 1 hour post thaw (not 3 hours as previously suggested). Second, patient age plays directly into the formula for success: patients over the age of 35 were less likely to achieve or maintain a stable spindle with appropriately aligned chromosomes when compared to cohort counterparts who were under the age of 35. Moving forward with oocyte cryopreservation will demand a careful look at the influence of maternal age.

Just how far-reaching is this topic with regard to the rapidly emerging field of fertility preservation and applications that will extend into more remote but no less contentious domains of reproductive medicine? Consider the paper by Gonzales et al. in this issue that draws attention to the combination of technologies aimed in the long run to provide as many options as possible to cancer patients. They report on the adoption of immature oocyte cryopreservation by vitrification in combination with in vitro maturation, protocols that in tandem offer compromises in oocyte and embryo quality that we do not yet fully understand. But the spirit and indication is there to seek optimization of individual technologies that when melded will present new opportunities to patients facing direct threats to their future reproductive competence.

And finally, as illustrated on our cover this month, studies from the laboratories of Combelles and her colleagues compare vitirifcation and slow freezing in immature human oocytes as a first approximation for storing these more primitive versions of the female germ cell. Using survival, maturation, and fertilization as outcome measures, they find a slight advantage for vitrified immature oocytes when compared to slow frozen ones, the latter of which exhibit a higher propensity to undergo spontaneous activation during subsequent culture for IVM.

Collectively, what we see is that the time is right to proceed full speed with adoption of oocyte cryopreservation and as with most promising and highly anticipated techniques, the opportunity arrives to reflect and capitalize on the new knowledge that stands to be gained. We hope the JARG readership continues to benefit from these and other developments and look forward to working with you in achieving a new age of human ARTs that might not have become available for our patients.