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Are We Ready to Eliminate the Transfer of “Fresh” Embryos in IVF?

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The practice of assisted reproductive technology has gone through waves of optimization and innovation. Since the landmark birth of Louise Brown demonstrating the feasibility of in vitro fertilization, we have seen the advent of multiple follicular stimulations, improvements in egg retrieval, the advent of intracytoplasmic sperm injection, dramatic improvements in culture conditions, a move towards extended embryo culture, and dramatic improvement in cryopreservation of eggs and embryos. Optimization of stimulation protocols, better selection of patients, and optimization of laboratory techniques have contributed to overall greater success rates as well as a greater number of high quality embryos to cryopreserve. Currently there is a trend toward cryopreservation of all embryos after IVF with transfer of a thawed embryo in a subsequent cycle. The rationale is that transfer of an embryo into a more “physiologic environment” will result in greater pregnancy rates and potentially decrease both maternal and perinatal morbidity. The clinical and translational rationale for this transition is compelling, but not proven. Is this the new breakthrough in the practice of assisted reproductive technology? Will this result in a dramatic change in practice?

The theorized preference for transfer of embryos into a more physiological hormonal milieu stems from an extension of the Barker Hypothesis. The Barker Hypothesis was generated suggesting that in utero stress may affect childhood development and propensity to adult disease. The consequences of ovarian stimulation associated with in vitro fertilization may suggest that the Barker Hypothesis should be extended to peri-conceptual events. Said another way, health at the time of or even before conception may affect in utero development, childhood development and predisposition for adult disease. Reproduction affects health and health affects reproduction (1).

IVF was designed to allow women with tubal factor infertility a chance to conceive. However, ovarian stimulation resulting in multiple eggs, and thus multiple embryos, has allowed expansion of indication to situations when we do not know the etiology of

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subfertility (2). The ability to work with multiple embryos is likely one of the reasons for higher pregnancy rates with IVF compared to an unstimulated cycle. However, ovarian stimulation may have unintended consequences. As many aspects of IVF-ET have been optimized, other aspects like possible alternations in endometrial development, early embryo development, implantation and/or early placentation have become the focus of modifiable factors that may further enhance safety and success.

The consequences of ovarian stimulation have been evaluated by comparing the perinatal outcomes in children conceived after a frozen transfer to those conceived with a fresh transfer (3). The growing body of evidence to support measurable and modifiable risk to children conceived with IVF is comprehensively reviewed (4). There are currently a number of purported rationales to the benefit of transferring embryos into a more physiologic rather than a hyperstimulated environment. Justifications include decreasing the risk of ovarian hyperstimulation syndrome, decreasing perinatal morbidity, and decreased maternal morbidity. Other benefits of “freeze all” include the possibility of genetic testing and a separation of embryo transfer from the stress and rigors of ovarian stimulation providing a more objective decision to transfer fewer embryos (or a single embryo).

There is also evidence to support greater success rates with transfer of a frozen thawed embryo. However, this evidence is complicated by differing selection of candidates to offer “freeze all,” the stage of development at cryopreservation, and the techniques used. Moreover, some of the evidence has been called into question due to impropriety regarding published studies. One of the two randomized trials on this subject has been retracted at the request of the Editor and the ASRM Publications Committee, based on the results of an investigation which found serious methodological flaws in the study (5).

If there is a detrimental effect of a supraphysiological environment to embryos and placentation, the mechanism of action is only beginning to emerge. It is naïve to say that this is all simply related to estrogen levels. Even if estrogen levels are an appropriate surrogate marker for other molecular changes, to date we do not know at what threshold a cycle becomes “supraphysiologic.” One unanswered question is if supraphysiologic conditions result with the use of gonadotropins (at any dose), or if alternations occur only when stimulation threshold has been exceeded? Of course, like most aspects of medicine, response is likely to vary in individual patients.

Any change in practice away from the transfer of fresh embryos must be considered in the face of disadvantages of cryopreservation. The absolute number of frozen embryo transfers is clearly on a rise. Currently, the live birth rate after a frozen embryo transfer is similar compared to the success rate after the transfer of a fresh embryo. However, there may be a downside of cryopreservation such as cost, time, convenience and possibly altering embryo competence and subsequent implantation and/or development. More evidence regarding the effects of cryopreservation (especially as techniques evolve) is needed. Clearly, our goal is not to shift one set of unintended consequences for another set.

Because we are already moving toward a greater use of frozen thawed embryos we must understand and amend the way we report success rates. When the transfer of embryos is no

longer linked to a single retrieval, reporting success is complicated and can be gamed. The SART CORS database was designed years ago when fresh embryo transfer almost always coincided with stimulation. The SART committee has grappled with how the concept of freezing embryos, be it elective or for banking purposes, has effected reporting. Reporting of success rates needs to be transparent and easily understood by our patients. SART has proposed changes in the reporting of outcomes.

The question regarding the benefit of cryopreservation of all embryos with subsequent replacement in more physiologic cycles is not without controversy. As is the case when new hypotheses are generated, it is hard to filter through the early studies to determine whether there is a publication bias, bias and confounding due to patient selection, or unconscious (or conscious) reporting of only favorable results. Currently the biological and physiologic changes of ovarian stimulation are being investigated with outstanding research. There are ongoing investigations regarding effects on the window of implantation, gene expression, and epigenetic phenomenon. There are also proposed randomized trials in the United States and in Europe to provide objective evidence to inform this debate. Optimally dramatic changes in the practice of medicine should be evidence based. However, often the practice of medicine moves before definitive evidence is obtained. In this case we need to make sure we interrogate the evidence continuously.

Time, and hopefully high quality research, will establish if we are ready to eliminate the transfer of “fresh” embryos in IVF. However, practice is already shifting. In this series of articles we review how cryopreservation of human embryos has contributed to IVF success rates, the rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer is examined from a clinical and translational standpoint, and the implication to ART registry and reporting.

References

1. Barnhart KT. Epidemiology of male and female reproductive disorders and impact on fertility regulation and population growth. *Fertil Steril*. 2011; 95(7):2200–2203. [PubMed: 21481377]
2. Kamphuis EI, Bhattacharya S, van der Veen F, Mol BW, Templeton A. Evidence Based IVF Group. *BMJ*. 2014; 348:252. 2014.
3. Kalra SK, Ratcliffe SJ, Coutifaris C, Molinaro T, Barnhart KT. Ovarian stimulation and low birth weight in newborns conceived through in vitro fertilization. *Obstet Gynecol*. 2011; 118:863–71. [PubMed: 21934450]
4. Pinborg A, Wennerholm UB, Romundstad LB, Loft A, Aittomaki K, Soderstrom-Anttila V, et al. Why do singletons conceived after assisted reproduction technology have adverse perinatal outcome? Systematic review and meta-analysis. *Human reproduction update*. 2013; 19:87–104. [PubMed: 23154145]
5. Retraction Note to: Can fresh embryo transfers be replaced by cryopreserved-thawed embryo transfers in assisted reproductive cycles? A randomized controlled trial. Aflatoonian, Abbas; Oskouian, Homa; Ahmadi, Shahnaz; Oskouian, Leila. *Journal of Assisted Reproduction & Genetics*. Sep.2013 30(9):1245. [PubMed: 23975193] . Retraction to: *J Assist Reprod Genet*. 2010; 27:357–363. [PubMed: 20373015]