Recurrent implantation failure is another indication for the freeze-all strategy

Magdi and colleagues (1) provide an interesting and timely report of a prospective quasi-randomized controlled clinical trial comparing a freeze-all strategy to a fresh transfer strategy in 171 patients diagnosed with recurrent implantation failure in a 30-month period. Cryopreservation was by blastocyst vitrification and the main outcome measure was ongoing pregnancy at 20 weeks of gestation. In this study (1), 38.4% of patients in the freeze all group achieved ongoing pregnancy, as did 20.7% of patients in the fresh transfer group. This difference was statistically significant. Comparisons of secondary measures found significant differences in pregnancy rate, implantation rate, and clinical pregnancy rate, all favoring the freeze-all group, but no significant difference in the rate of early pregnancy loss. The rate of multiple pregnancy in the freeze-all group was significantly greater than in the fresh group, suggesting that, in routine clinical practice, the number of embryos transferred should be moderated in order to compensate for the greater implantation rate (40.0% vs. 16.0%) with thawed embryos than with fresh embryos in these patients.

The findings of Magdi and colleagues (1) are consistent with a previous retrospective study in patients with prior implantation failure with fresh blastocysts (2). In this prior study (2), the cryopreservation technique involved slow-frozen 2pn oocytes cultured to the blastocyst stage before transfer. Despite substantial methodological differences, both studies found that their main outcome measures, ongoing pregnancy or live birth rates, were approximately doubled with freeze-all, and that implantation rates were improved by a factor of about 2.5. The close agreement of these two studies (1, 2) makes their conclusions more convincing, although Magdi et al. (1) are certainly correct that a large randomized trial would still be beneficial. The Shapiro et al. study also included an intention-to-treat analysis of live birth rates per retrieval and cumulative live birth rates per retrieval, and again found significant differences in favor of freeze-all.

To date, the freeze-all strategy has been reported to be superior in multiple patient populations, including those with polycystic ovary syndrome, use of gonadotropin-releasing hormone agonist "trigger", delayed blastulation, elevated pre-ovulatory progesterone, advanced age, those using preimplantation genetic screening, and those with prior fresh blastocyst implantation failure (3). Magdi et al. (1) introduces recurrent implantation failure with fresh embryos as another indication for freeze-all. Interestingly, no prospective study has identified a population or group for which fresh autologous transfer has superior success rates.

It seems very likely that patients with repeated failed fresh transfers are a selected sub-group with significantly increased risk of impaired endometrial receptivity following ovarian stimulation, among other issues. If all the patients treated by Magdi and colleagues (1) had received freeze-all from the outset, it seems likely these patients destined for recurrent failure could have had earlier success, and no known subgroup would have had reduced success rates. There is increasing doubt that fresh autologous transfer should remain the default standard (3).

Current arguments in favor of fresh autologous transfer include the contention that immediate fresh transfer hastens pregnancy. Despite limited intuitive appeal, there is no evidence to support the hypothesis that time-to-pregnancy is reduced by fresh transfer. Another is the hypothesis that fresh transfer must reduce cost-per-pregnancy because it reduces cost-per-cycle. However, this hypothesis is contrary to published reports of reduced cost-per-pregnancy with freeze-all when compared to fresh transfer (4).

As early as 1977, even before the first live birth from in vitro fertilization, Edwards and Steptoe (5) attributed implantation failures to "abnormal endocrine conditions arising in patients treated with HMG and HCG." They discussed the advantages of avoiding the negative effects of uterine exposure to ovarian stimulation by freezing all embryos for subsequent transfers of single frozen-thawed embryos. Alas, the cryo-technology of the period was poor, and their first in vitro fertilization infant resulted from a fresh transfer. Fresh transfer then became the default standard.

It is interesting to ponder that if freeze-all had somehow become the initial default standard treatment, whether the evidence available today would support a migration to fresh transfer. This seems doubtful, given the absence of prospective studies finding superior success rates with fresh transfer.

Magdi et al. (1) reported an increased multiple pregnancy rate per transfer (23.5% vs. 8.9%) with thawed embryo transfers than with fresh embryo transfer. They conclude that the freeze-all group should have had fewer transferred embryos, and that elective single embryo transfer would have been valuable in patients undergoing freeze-all, even in this challenging group with recurrent prior implantation failure. This finding fits nicely with the growing paradigm of universal single embryo transfer to avoid multiple gestation and its associated increased health risks.

Bruce S. Shapiro, M.D., Ph.D.[a,b]
Forest C. Garner, M.S.[a,b]
[a] Fertility Center of Las Vegas; and [b] Department of Obstetrics and Gynecology, University of Nevada School of Medicine, Las Vegas, Nevada

http://dx.doi.org/10.1016/j.fertnstert.2017.05.018

You can discuss this article with its authors and with other ASRM members at https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/16795-24329

REFERENCES

1. Magdi Y, El-Damen A, Fathi AM, Abdelez AM, Youssef MAE, et al. Revisiting the management of recurrent implantation failure through freeze-all policy. Fertil Steril 2017;118:72–7.
2. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Freeze-all can be a superior therapy to another fresh cycle in patients with prior fresh blastocyst implantation failure. Reprod Biomed Online 2014;29:286–90.
3. Shapiro BS, Daneshmand ST, Garner FC, Aguirre M, Hudson C. Clinical rationale for cryopreservation of entire embryo cohorts in lieu of fresh transfer. Fertil Steril 2014;102:3–9.
4. Roque M, Valle M, Guimarães F, Sampaio M, Geber S. Cost-Effectiveness of the Freeze-All Policy. JBRA Assist Reprod 2015;19:125–30.
5. Edwards RG, Steptoe PC. The relevance of the frozen storage of human embryos. Ciba Found Symp 1977;52:235–50.