Whether immediate frozen-thawed embryo transfer improves IVF outcome in non-elective freeze all policy

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With the spread of vitrification techniques, the survival rate after thawing of embryos rapidly increased, reaching up to 90% for vitrified blastocysts (1). As a result of the advances in embryology laboratory techniques, the “segmentation” of in vitro fertilization (IVF)-embryo transfer cycles has been gradually introduced in the common practice as an alternative to fresh IVF for the protection of woman’s health and to improve the chances of implantation (2).

Non-elective freeze all policy is currently indicated in case of unforeseeable complications occurring during controlled ovarian stimulation (COS) (e.g., unexpected hyper-response, hyperprogesteronemia, endometrial abnormalities) or before embryo transfer (i.e., patients’ fever and other illnesses). The principal question that remains unanswered concerns the optimal timing of frozen-thawed embryo transfer (FET) after COS. In this respect, the study by Huang et al. (3) heats up the debate on the possible advantages of immediate FET following non-elective freeze all cycles.

In their retrospective study, the authors included 2,998 patients who underwent their first FETs after the first COS cycles using the non-elective freeze-all strategy. Patients were divided into the “immediate” group (i.e., FET performed within the first menstrual cycle after COS), and the “delayed” group where FET started after one or more menstrual cycles following COS. As a statistical solution to the problem of endogeneity between groups, the authors used the propensity score adjustment of confounders, thereby increasing between group comparability. After confounders adjustment, delayed FET after COS was associated with significantly decreased chances of clinical pregnancy (OR: 0.46–0.94), ongoing pregnancy (OR: 0.42–0.84) and live birth (OR: 0.42–0.85) than immediate transfer, as well as with higher risk of miscarriage (OR: 1.05–8.06).

These interesting findings upon superiority of immediate transfer compared to delayed transfer were in line with one previous study (4), but contradicted other studies (5-10) that reported not significant differences between immediate and postponed embryo transfer. However, we cannot make direct inferences between studies as they applied different methodology (including differences in the protocols adopted and time intervals between oocyte retrieval and FET), and included patients with different characteristics.

To the credit of Huang et al. (3), theirs was the largest cohort size among the studies on this topic. Moreover, the use of propensity score matching may have minimized the selection bias over conventional multivariable regression techniques, therefore providing robustness to their results. Although the results were exciting, the underlying mechanism for the association between earlier timing of FET and higher success at IVF need to be further investigated. Basing on the findings of the study by Huang et al. (3), it may be speculated that COS leaves a transient hormonal footprint with positive effects on endometrial receptivity. In this respect, the persistence of active
corpora lutea following COS could enhance the circulating concentrations of several ovarian hormones, such as relaxin, during FET cycle (11). Alternatively, supraphysiologic hormonal stimulation during COS may positively modulate the expression of specific endometrial genes during the following menstrual cycle (12), similarly to what observed in women after endometrial mechanical stimulation (8,13).

The findings by Huang et al. (3) are intriguing but not definitive. Observational data, even though analyzed with statistically efficient techniques, need to be confirmed by randomized controlled trials for proving cause-and-effects relationships between two phenomena. Therefore, future randomized controlled trials, with strict inclusion criteria and rigorous methodology, are urgently needed.

Thanks to the efforts of Huang et al. from now on, immediate FET after COS can be considered as a valuable alternative to delayed FET. Until solid evidence will be available, physicians are advised to schedule FET based on clinical circumstances and after comprehensive patients’ consultation.

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Footnote

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