Editorial

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

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Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Comment on: Huang J, Lu X, Xie Q, *et al*. Timing of frozen-thawed embryo transfer after controlled ovarian stimulation in a non-elective freeze-all policy. Ann Transl Med 2019;7:752.

Submitted Apr 19, 2020. Accepted for publication May 09, 2020.

doi: 10.21037/atm-2020-97

View this article at: http://dx.doi.org/10.21037/atm-2020-97

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.

Acknowledgments

Funding: None.

Footnote

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-2020-97). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Marin L, Vitagliano A. Whether immediate frozen-thawed embryo transfer improves IVF outcome in non-elective freeze all policy. Ann Transl Med 2020;8(16):979. doi: 10.21037/atm-2020-97