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LETTER TO EDITOR

Serum progesterone levels on day of embryo transfer in frozen embryo transfer cycles—the truth lies in the detail

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We read with interest the recent publication "Do serum progesterone levels on day of embryo transfer influence pregnancy outcome in artificial frozen-thaw cycles?" by Volovsky et al. (2020). The study included a total of 2010 hormonal replacement therapy frozen embryo transfer (HRT-FET) cycles and to our knowledge, this is the largest retrospective cohort study, correlating serum progesterone (P4) levels on the day of embryo transfer to reproductive outcomes.

A threshold of 10 ng/mL was used in accordance with the most recently published literature and biochemical pregnancy, clinical pregnancy, and live birth rates were compared between those patients with P4 levels above and below this threshold.

When comparing FET outcomes in relation to P4 levels < 10 ng/mL and ≥ 10 ng/mL, the authors observed no differences in any reproductive outcome parameters, and from their analysis, the authors conclude that "serum P4 levels at or above 10 ng/mL (31.8 nmol/l) do not confer a statistically significant improvement in pregnancy outcomes." However, they reported a critical threshold of 5 ng/mL below which live birth rates decreased significantly [1].

Interestingly, the results of this study are diametrically opposed to previously published studies in HRT-FET using vaginal progesterone for luteal phase support [2–7] as all the referenced studies reach the opposite conclusion: peri-implantation serum P4 levels significantly impact reproductive outcomes of the HRT-FET cycle. Importantly, two of these studies are prospective studies including a total of 1400 patients [5, 6].

When scrutinizing the Volovsky et al. publication, however, a crucial and important flaw appears, as additional exogenous progesterone was supplemented in all patients with serum P4 levels less than 8 ng/mL. Thus, an intervention aiming at increasing serum P4 was actively performed on the day of embryo transfer so-called luteal rescue in low P4 cases. The authors mention this flaw in the Materials and Methods by stating that "if levels were less than 8 ng/mL, then P4 replacement was increased at the discretion of the treating clinician." This rescue action obviously from a physiological point of view most certainly could explain why no difference was seen in reproductive outcomes between patients with P4 levels < 10 ng/mL and ≥ 10 ng/mL. The authors do mention this issue in the Discussion; however, they still conclude that serum levels above 10 ng/mL do not improve pregnancy outcomes.

Regrettably, the authors account for neither the type of progesterone supplementation used in these cases nor the dose or route of administration (vaginal, intramuscular, subcutaneous, oral, or rectal). The fact that additional progesterone was added in low serum P4 cases makes a crucial difference for the outcomes of this retrospective study—which in reality was an interesting "interventional study" and which definitely does not suggest that low P4 level patients perform similar to normal P4 level patients.

However, we agree with Volovsky et al. that serum P4 levels and the intra-endometrial P4 levels depend on the route of administration. The most optimal serum P4 cutoff level might be different, depending on the type, dose, and route of administration used, and more studies are needed to identify the most optimal HRT-FET protocol and how to individualize luteal progesterone treatment according to serum P4 levels.

Until further evidence is available, the majority of recent studies agree that serum P4—as a proxy of intra-endometrial P4—has a significant impact on the reproductive outcome of an HRT-FET cycle.

After close reading the Volovsky et al. paper, we suggest that the authors from their retrospective analysis should have concluded that measuring serum P4 is of clinical importance

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and that treating patients with low serum P4 levels with additional progesterone seems to increase the reproductive outcome of the HRT-FET cycle.

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