Risk of preeclampsia in artificial frozen embryo transfer as a result of insufficient corpus luteum hormone levels: a response

We thank Dr Al-Lami for her interest in and comments on our recent Clinical Opinion titled "Potential role of the corpus luteum in maternal cardiovascular adaptation to pregnancy and preeclampsia risk"[1]. The concept that preeclampsia risk is increased in frozen embryo transfer cycles—specifically artificial cycles (FET-AC)—is largely based on observational studies, though randomized clinical trials (RCTs) are currently in progress. Even if RCTs corroborate this link, however, the underlying mechanisms will be difficult to prove without further interventional studies. Nevertheless, we wholeheartedly agree with Dr Al-Lami that it is important to be open-minded about the potential underlying mechanisms, including the immunomodulatory effects of circulating sex steroids—the concentrations of which may be suboptimal, and of circulating relaxin, as well as other CL factor(s)—which are not replaced, and therefore, completely absent in FET-AC.

In our work, the plasma estradiol concentrations were, on average, comparable among the women conceiving with or without a corpus luteum (CL).[2,3] The circulating progesterone concentrations were also comparable throughout the first trimester in our investigations, where maternal cardiovascular changes during early pregnancy were found to be attenuated in women who conceived without a CL.[2] In contrast, most likely owing to the vaginal administration of progesterone, the plasma concentrations were lower in our study, which demonstrated increased preeclampsia risk in women who conceived using FET-AC.[3] Nevertheless, even if the circulating concentrations of administered sex steroids are considered to be within the "normal" range in AC, they may still be inadequate to promote optimal (pre)decidualization in a subset of women. Because inadequate (pre)decidualization may be a precursor of preeclampsia[4] and CL products are the master regulators of (pre)decidualization, then perhaps, suboptimal luteal support with sex steroids and the absence of other CL hormones such as relaxin predispose women conceiving without a CL to preeclampsia, as in FET-AC (provided in the Summary Figure 7 in our Clinical Opinion). The precise cellular and molecular abnormalities underlying suboptimal (pre)decidualization are likely to be multifactorial. However, because the modulation of immune cell number and phenotype is a part and parcel of (pre) decidualization, perturbation of the normal uterine immune milieu is likely in FET-AC, as suggested by Dr Al-Lami.

The concept that the antecedents of preeclampsia may reside in aberrant corpus luteal or endometrial function—at least in a subset of women who develop the disease—is admittedly a relatively new and underdeveloped area of research in reproductive sciences. Therefore, there are still many unanswered questions, and we encourage further research along these lines. ■

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