Immune-altering roles of progesterone and subsequent development of preeclampsia in artificial cycles of frozen embryo transfer

TO THE EDITORS: Conrad et al[1] discussed in detail the possible risk factors for the development of hypertensive disorders of pregnancy (HDP) among women conceived by frozen embryo transfer cycles, specifically preeclampsia development in artificial cycles (frozen-thawed embryo transfer artificial cycle [FET-AC]). They discussed the role of relaxin and also suggested the possible role of suboptimal hormonal levels in the development of preeclampsia and HDP in women conceived by FET-AC. The process of decidualization and normal placentation is strictly controlled by certain levels of various inflammatory markers, the disruption of which may lead to abnormal placentation.[2] Less-than-physiological levels of estrogen and progesterone in FET-AC may contribute to improper decidualization and subsequent abnormal placentation, which could lead to placental ischemia and preeclampsia development later in pregnancy. Previously, we have explained the possible immune-altering roles of less-than-physiological levels of estrogen in the development of preeclampsia and placenta accreta spectrum in women conceived by FET-AC.[2,3]

Suboptimal levels of progesterone may also contribute to abnormal decidualization and potentially to preeclampsia development in FET-AC through immune response alteration. Normally in pregnant women, endogenous progesterone can modulate the function of the innate and cellular immune response systemically and locally in the maternal−fetal interface and exhibit a net anti-inflammatory effect for successful pregnancy.[4] It was found that progesterone can inhibit the activation of various inflammatory cells (including uterine macrophages), suppress the nuclear factor kappa B signaling pathway, increase anti-inflammatory cytokines (eg, interleukin-10), and decrease proinflammatory ones (eg, tumor necrosis factor-α).[4] Further, progesterone favors a T helper type (Th)-2 response over a Th-1 response, with a subsequent heightened humoral response rather than a T-lymphocyte cellular immune response, which subsequently mitigates the inflammatory reaction.[4] It is thus reasonable that suboptimal levels of progesterone (as found in FET-AC) may lead to improper decidualization, placental ischemia, and preeclampsia development in addition to tolerance failure to paternal antigens and augmented inflammatory response, which collectively results in a higher risk of HDP and preeclampsia. It is therefore interesting to know and would be appreciated if Conrad and colleagues[1] can discuss other potential pathways through which suboptimal hormonal levels contribute to the development of HDP and preeclampsia in women conceived by FET-AC in addition to the hormones' immune-altering roles that affect decidualization and subsequent placentation and their synergistic effects with relaxin. ■

Rasha A. Al-Lami, MD, MS-CS
Department of Obstetrics, Gynecology and Reproductive Sciences
McGovern Medical School
The University of Texas Health Science Center at Houston
6431 FanninHouston, TX 77030
Rasha.A.AlLami@gmail.com

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