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LETTER TO THE EDITOR

Is a frozen embryo transfer in a programmed cycle really the best option?

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Cryopreservation of human embryos with subsequent frozen-thawed embryo transfer (FET) increased from 7.9% of embryo transfers in 2004 to 40.7% of embryo transfers in 2013 in the United States (US), with similar increases globally [1–3]. Despite the increasing popularity of FET, emerging data have raised concern because of the observed increased risk of hypertensive disorders of pregnancy following FET [4–12]. These data are troubling due to preeclampsia's associated severe adverse consequences on the short- as well as on the long-term health for mothers and infants.

Several questions arise. What are the reasons for this increase in the risk of preeclampsia with FET? Would the association between FET and hypertensive disorders of pregnancy be observed in a large cohort? A recent observational study from Sweden that included nearly 10,000 singleton pregnancies achieved via FET detected an increased risk of hypertensive disorders in programmed FET cycles, but not in natural or stimulated FET cycles [13]. This Swedish study supported the prospective observational cohort study from the USA [14]. In the latter study, programmed cycles (corpus luteum [CL] absent) were associated with significantly higher rates of preeclampsia (12.8% vs 3.9%, $P = 0.02$) and preeclampsia with severe features (9.6% vs 0.8%, $P = 0.002$) compared with modified natural FET cycles (CL present). Regression analysis including adjustments for nulliparity, age, prior history of hypertension, body mass index, diabetes (pre-gestational and gestational), and polycystic ovary syndrome (PCOS) confirmed a significantly increased risk of preeclampsia in the absence of the CL [14].

Thus, emerging observational data suggest that protocol choice, specifically the use of protocols that do not result in the formation of a CL may, at least in part, explain the increased risk of preeclampsia associated with FET [13, 14]. FET is commonly performed in a programmed cycle in which the ovaries are suppressed, and the endometrium is prepared using exogenous estradiol and progesterone, in part because such a protocol allows maximum flexibility in scheduling. These observational data implicating the absence of a CL with an increased risk of hypertensive disorders of pregnancy are supported by detailed assessment of maternal vascular physiology reported in two separate US populations [14, 15]. The absence of the CL was associated with attenuation of the expected decline in carotid-femoral pulse wave velocity and rise in carotid-femoral transit time during the first trimester [14]. Women lacking a CL did not have the expected drop in mean arterial blood pressure in pregnancy, had a lower reactive hyperemia index, and had a higher augmentation index compared with pregnancies achieved with the CL present [15]. The number of angiogenic and non-angiogenic circulating endothelial progenitor cells were both lower in the absence of a CL [15]. Furthermore, an absent CL has also been associated with higher creatinine, sodium, and total carbon dioxide levels in early pregnancy [16], compared with the presence of the CL.

Why would the absence of the CL be associated with deficient maternal circulatory adaptation in early pregnancy and an increased risk of preeclampsia? One potential explanation is that the programmed cycles with absent CL do not fully reproduce the physiologic conditions of early pregnancy, a

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theory initially proposed by Conrad [17, 18]. The CL produces vasoactive products such as relaxin and vascular endothelial growth factor (VEGF); however, in a programmed cycle, only estradiol and progesterone are exogenously replaced. Relaxin is undetectable during early pregnancy in programmed cycles [16], and relaxin has long been thought to have a physiologic role in normal pregnancy [19]. Given that vascular dysfunction predates clinical presentation of preeclampsia and is considered to be part of the pathogenesis [20–28], it is biologically plausible that the increased preeclampsia risk in programmed FET pregnancies may be at least partly attributable to the impact of absent CL on the maternal hormonal environment and circulatory function in the first trimester.

Given the myriad of negative health consequences associated with preeclampsia [29–35] and the high utilization of FET, it is critical to minimize the increased risk of preeclampsia that is associated with FET. The emerging data beg the question: is a frozen embryo transfer in a programmed cycle really the best option? The answer to this question will require a randomized clinical trial comparing programmed FET with a more physiologic protocol where CL function is preserved.

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Compliance with ethical standards

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