Endometrial thickness as an independent risk factor for ectopic pregnancy in in vitro fertilization: should we change our counseling and practice?

In this issue of Fertility and Sterility, Liu et al. (1) analyzed the effect of endometrial thickness (EMT) on ectopic pregnancy rate in frozen embryo transfer (FET) cycles. Ectopic pregnancy (EP) is an undesired outcome of in vitro fertilization (IVF) cycles and has significant medical, emotional, and financial implications for the patients. Large studies that have analyzed more than 10 years of data in United Kingdom and United States show that the risk of ectopic pregnancy associated with IVF is 1.5% to 2%, and it has decreased over time (2, 3). This risk appears comparable to U.S. general population. However, the results of individual investigations vary and EP rates appear to be higher (2%–5%) in some studies—mostly from China (4). There are many known risk factors for EP, including smoking, tubal disease, pelvic adhesions, previous ectopic pregnancy, multiple embryo transfer, fresh and cleavage-stage embryo transfers.

Liu et al. (1) performed a retrospective cohort study examining 17,244 FET cycles that resulted in pregnancy, from a single institution over 8 years time period. Liu et al. (1) concluded that, after adjusting for known risk factors of ectopic pregnancy, EMT remains a significant independent risk factor for EP. All analyzed cycles had EMT of at least 7mm on the day of progesterone start or the day of hCG trigger. EP rate was inversely proportional to EMT. Interestingly, medicated FET was associated with higher EP risk compared to modified natural or stimulated cycles.

Large sample size is the strength of the study. Moreover, the data was collected in a single center which decreases differences in clinical and laboratory practices and reduces operator-dependent variations in sonographic assessments. The evaluation of only FET cycles also avoids heterogeneity associated with fresh cycles. However, the study has several limitations, some of which are inherent to the retrospective design. In 785 cycles, there was either unknown outcome or no EMT data recorded. Omission of this missing data may introduce selection bias. Liu et al. (1) suggest that they did not have data on smoking which is a known confounder. Moreover, not all confounding variables may have been accounted for due to possible unknown factors affecting ectopic pregnancy pathogenesis. Liu et al. (1) define thin EMT as <8 mm in FET cycles, however, most prior studies define thin endometrium as less 8mm in fresh cycles and less 7 mm in FET cycles. This is an important clarification to make while interpreting the results of this study. However, this does not affect the results or proposed mechanism of ectopic pregnancy pathogenesis in the current study.

Higher EP rate (3.15%) limits the generalizability of the study findings to Western populations, which have much lower EP rate after IVF as discussed above (1.5%–2%). Liu et al. (1) attribute higher EP numbers in this study to the high rate of tubal factor infertility in their population (42.8%). Another variation in practice was their embryo selection process which aimed to freeze high grade cleavage stage embryos. Embryos with suboptimal morphology were cultured further, and frozen if reached blastocyst stage and had good morphology. Most embryos were transferred at cleavage stage (86%). This is different from most programs in the West which exclusively freeze blastocysts. Although Liu et al. (1) have accounted for increased EP rate with cleavage-stage embryo transfers in their analysis, this difference in practice may further limit applicability of their findings to Western populations. Moreover, the majority of cycles in this study were stimulated FET cycles (47%) and had 2 embryos transferred (86%), which is also different from most centers in North America.

Liu et al. (1) discuss that their findings contradict proposed mechanism by Rombauts et al. (5) on how EMT affects uterine peristalsis. On the contrary, subsequent publication from the same group and the discussion of their findings are in line with the conclusions from this study. Rombauts et al. (5) have demonstrated that increased endometrial thickness is associated with placenta previa and thin endometrium is associated with EP. They suggest that the direction of uterine peristalsis is of utmost importance and EMT is a marker of fundus-to-cervix uterine peristalsis (5).

This is the second large retrospective study that points to the role of EMT as an independent risk factor for EP (1, 5). Liu et al. (1) propose that the results from these studies can help with patient counseling. They suggest that in patients with multiple risk factors for ectopic pregnancy, such as prior EP, medicated FET and smoking, endometrial thickness can be a tipping point in decision making. However, given the limitations above and questions regarding generalizability of the findings, further prospective studies are needed before this study can change practice.

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