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Title:

THE EFFECT OF SUPRAPHYSIOLOGIC ESTRADIOL LEVELS ON PREGNANCY OUTCOMES IN SINGLE EUPLOID FROZEN EMBRYO TRANSFER CYCLES

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Objective:

In the United States, frozen embryo transfers (FETs) after in vitro fertilization (IVF) cycles have increased by >80% since 2006. Patients undergoing controlled ovarian hyperstimulation are often exposed to supraphysiologic levels of estradiol (E2), which have been associated with increased uterine contractility, dyssynchrony between endometrial and embryo development, and decreased implantation rates in fresh IVF cycles. A recent study of elevated E2 levels during FET showed an association with decreased ongoing pregnancy/live birth rates (OP/LBR). However, that study was confounded by transfer of multiple unscreened embryos and small sample size. This study evaluates the association between supraphysiologic E2 levels and pregnancy outcomes in a single euploid FET model.

Design:

Retrospective cohort analysis

Materials and Methods:

The study included patients undergoing single euploid FET from 2012 to 2019. Endometrial preparation was performed using oral, vaginal, transdermal E2, or a combination of these routes. Cycles involving ovum donation, natural endometrial preparation, intramuscular E2, >21 days of

E2 stimulation, or an endometrial thickness <8 mm were excluded. Preimplantation genetic testing for aneuploidy (PGT-A) was performed using quantitative polymerase chain reaction, array comparative genomic hybridization or next generation sequencing. Supraphysiologic E2 levels were defined as the mean+2SD E2 of natural FET cycles occurring in the same time period. E2 exposure was measured using area under the curve (AUC). Supraphysiologic E2 was calculated as AUC E2 ≥ 7,136.4 pg/mL. The primary outcome of the study was OP/LBR. Secondary outcomes included clinical pregnancy (CP) and early pregnancy loss (EPL) rates. Data were evaluated using t-tests, chi-square tests, and generalized estimating equations.

Results:

The study included 3876 single euploid FET cycles from 2707 patients. CP and OP/LBR were 61.9% and 54.1% in the physiologic E2, and 53.9% and 47.3% in the supraphysiologic E2 groups, respectively. Univariate analysis identified BMI and embryo morphology ≥4BB as possible confounders. After controlling for these confounders, there was a decreased CP rate in cycles that had supraphysiologic compared to physiologic E2 levels (OR 0.72 [95% CI 0.52-0.99], p=0.04), but no difference in OP/LB rate (OR 0.78 [95% CI 0.57-1.06, p=0.12), or EPL rate (OR 1.16 [95% CI 0.77-1.74], p=0.47).

Conclusion:

In this study evaluating the association between E2 levels and pregnancy outcomes in a single euploid FET study model, we found that CP, but not OP/LBR, is significantly lower in the presence of supraphysiologic E2 levels. This study found no difference in biochemical or clinical pregnancy loss following FET of a euploid embryo in the setting of supraphysiologic E2, suggesting that patients can be reassured that after implantation there is no demonstrable increase in EPL. Future studies might focus on pharmacogenomic markers that can identify women who will respond to equivalent doses of E2 with higher serum E2 levels, to optimize the uterine environment for FET.