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Title:

INCREASING LUTEAL PROGESTERONE LEVELS ARE ASSOCIATED WITH HIGHER ONGOING PREGNANCY RATES AND LOWER EARLY PREGNANCY LOSSES FOLLOWING SINGLE EUPLOID FROZEN EMBRYO TRANSFER

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Objective:

Endometrial programming with exogenous estradiol (E2) and progesterone (P4) during a frozen embryo transfer (FET) cycle mimics the hormonal environment of a natural cycle, while allowing for synchronization of embryo and endometrial development. While studies have investigated the ideal timing of P4 initiation and the association of supraphysiologic E2 levels with FET and perinatal outcomes, less is known about how the level of P4 exposure impacts implantation and placentation. Prior research has suggested that elevated P4 levels during FETs are associated with a lower ongoing pregnancy/live birth (OP/LB) rate and higher early pregnancy loss (EPL) rate. Other studies have suggested an association between FETs and large for gestational age (LGA) and postdates infants. Yet, there is no known mechanism for these findings. The objective of this study is to determine whether the level of P4 exposure at time of FET and throughout the first trimester impacts FET or perinatal outcomes.

Design:

Retrospective cohort analysis

Materials and Methods:

The study included patients undergoing a single euploid FET at an academic center from 2012-2019. Luteal support methods other than intramuscular P4 were excluded. Serum P4 level was treated as a continuous variable. Peri-implantation P4 was defined as P4 level on the day prior to FET, and first trimester P4 was defined as average P4 from the day prior to FET until ~10 weeks of gestational age (GA). Primary outcomes were rates of OP/LB and EPL. Secondary outcomes were clinical pregnancy (CP) rate, GA at delivery, and neonatal birth weight. Small for GA (SGA)/LGA were defined using sex-specific data for the 10th/90thpercentile. Data were evaluated using univariate linear regressions with generalized estimating equations.

Results:

A total of 3773 single euploid FET cycles from 2699 patients were included. After controlling for age, BMI, endometrial thickness, embryo morphology, and days required for blastulation, there was a significant association between average P4 and OP/LB (OR 1.15 [95% CI 1.13-1.17], p <0.001), as well as EPL (OR 0.83, [95% CI 0.81-0.85], p<0.001). There was no association between peri-implantation P4 and CP rate. There was a significant decrease in GA at delivery with increasing P4 (β=-0.19 week, p<0.001). Mean first trimester P4 levels were not associated with birth weight after controlling for GA, fetal sex and BMI. There was no association between P4 and incidence of SGA/LGA infants.

Conclusion:

In a large cohort of single euploid FETs, we showed that luteal P4 in early pregnancy is positively correlated with OP/LB rate, and inversely correlated with EPL rate. While the level of exposure to P4 is crucial for pregnancy maintenance, increasing P4 levels in the first trimester do not appear to have downstream effects on placentation. Increasing luteal P4 level is associated with a shorter duration of pregnancy, but is not associated with differences in birth weight, or incidence of SGA or LGA infants. Future studies might focus on the pharmacogenomic profiles of women undergoing synthetic endometrial preparation with the aim of individualizing FET protocols.