ASSOCIATION OF ROUTE OF EXOGENOUS ESTROGEN ADMINISTRATION IN EUPLOID SYNTHETIC FROZEN EMBRYO TRANSFER CYCLES AND PREGNANCY OUTCOMES

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Background
For frozen embryo transfer (FET) cycles, there are three current methods to adequately prepare the endometrium for implantation: natural cycle (endogenous hormone production), stimulated (endogenous hormone production via oral medications or injectable gonadotropins), or synthetic (exogenous hormone administration). The evidence to support one method over another when considering implantation or live birth rate is not strong; however, more recent data suggests lower live birth rates and increased risk of adverse pregnancy outcomes in synthetic cycles. Possible posed explanations include the absence of a corpus luteum or the route of estrogen replacement. Unfortunately, available evidence to date has important limitations including comparing only two routes of estrogen, sample sizes ranging from 90-300 patients, unknown embryo ploidy status, a combination of day three and five FETs, and lacking live birth as the primary outcome.

Objective
To evaluate the association between the route of estrogen (oral, vaginal, transdermal, intramuscular) administration and cycle and pregnancy outcomes in those undergoing autologous single, euploid, synthetic FET.

Materials and Methods
This was a retrospective cohort study of autologous, single, euploid FET cycles using a synthetic protocol at a large academic fertility practice from October 2017 to December 2023. Cycles using autologous oocytes with IVF/ICSI created in January 2017 or beyond and PGT-A/M were included. Cycles using surgical sperm or gestational carriers, converted to natural or stimulated protocol, or with outcomes lost to follow up were excluded. The primary outcome was live birth (LB) after first FET. Secondary outcomes included chemical pregnancy, clinical pregnancy, and pregnancy loss. Chi-square, ANOVA, and Kruskal-Wallis were used for univariate comparisons. Multivariable logistic regression adjusting for maternal age, BMI, estradiol level, endometrial thickness, and embryo grading was performed for primary and secondary outcomes. $P < 0.05$ was considered statistically significant.

Results
11,804 autologous, single, euploid FET cycles using a synthetic protocol were included with 8,742 being first FET cycles. Of those, 11,065 (93.7%), 595 (5.0%), 50 (0.4%), and 94 (0.8%) cycles utilized oral, vaginal, transdermal, and intramuscular estrogen replacement, respectively. Maternal age at retrieval, AMH, day of blast, and embryo expansion grade were similar between groups; however, BMI, maternal age at transfer, estradiol level, endometrial thickness, and inner cell mass and trophectoderm grade were significantly different. The overall live birth rate was 56.9% in the entire cohort. After adjusting for confounders, there was a significant difference in the probability of LB (OR 0.48, 95% CI [0.30-0.78], p=0.003) and pregnancy loss (OR 1.05, 95% CI [1.10-3.44], p=0.022) in cycles with intramuscular estrogen supplementation compared to oral estrogen supplementation (Table 1). There were no differences in live birth or other pregnancy outcomes in the vaginal or transdermal estrogen groups when compared to oral

administration. However, when evaluating first FET cycles only, there was no difference in live birth or pregnancy loss between estrogen replacement groups in adjusted analyses.

Conclusions

For first autologous single, euploid, synthetic, FET cycles, there was no difference between probability of live birth or pregnancy loss between vaginal, transdermal, and intramuscular estrogen replacement compared to oral estrogen replacement.

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Table 1. Route of Estrogen Supplementation and Pregnancy Outcomes for First, Autologous, Single, Euploid, Synthetic FET

Route of Estrogen (n, %)	**Chemical Pregnancy Rate** (%)	**Adjusted* OR for Chemical Pregnancy** (OR, 95% CI)	**Clinical Pregnancy Rate** (%)	**Adjusted* OR for Clinical Pregnancy** (OR, 95% CI)	**Pregnancy Loss Rate** (%)	**Adjusted* OR for Pregnancy Loss** (OR, 95% CI)	**Live Birth Rate** (%)	**Adjusted* OR for Live Birth** (OR, 95% CI)
Oral (n=8,363, 95.7%)	79.4%	Reference	65.1%	Reference	24.3%	Reference	59.4%	Reference
Vaginal (n=305, 3.5%)	76.4%	1.16 (0.79-1.70)	54.8%	0.99 (0.72-1.37)	36.6%	1.28 (0.88-1.88)	47.5%	0.93 (0.67-1.28)
Transdermal (n=31, 0.3%)	83.9%	1.71 (0.63-4.63)	64.5%	1.23 (0.57-2.66)	30.8%	1.24 (0.53-2.89)	58.1%	1.17 (0.56-2.45)
Intramuscular (n=43, 0.5%)	55.8%	0.51 (0.26-0.99)**	32.6%	0.44 (0.22-0.87)**	41.7%	1.50 (0.63-3.55)	32.6%	0.55 (0.28-1.10)

*Adjusted for maternal age at egg retrieval, body mass index, maximum serum estradiol prior to exogenous progesterone, maximum endometrial thickness prior to exogenous progesterone, blastocyst day, expansion grade, inner cell mass grade, trophectoderm grade.

**Statistically significant ($p<0.05$)

OR: odds ratio, CI: confidence interval