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**Title**

# ENDOMETRIAL PREPARATION FOR FET: DOES THE DURATION OF ESTRADIOL SUPPLEMENTATION MATTER?

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**Objective:**
The sequential administration of estrogen (E2) and progesterone (P4) administration allows precise manipulation of endometrial growth to prepare for a frozen embryo transfer (FET) cycle. Findings from previous studies on ideal endometrial preparation regimens for FET may be confounded by the fact that they did not control for embryo quality or the number of embryos transferred. The exact limits of endometrial compliance and flexibility with which FETs can be scheduled remains unknown. This study evaluated whether the duration of estradiol supplementation in the follicular phase of an FET cycle impacts clinical outcome.

**Design:**
Retrospective, observational study

**Materials and Methods:**
The study included patients who underwent single, euploid FET from January 2012 to February 2017. Oral estradiol (E2) is administered at 2mg, twice per day, for 4 days; and thereafter, three times daily. Weekly transvaginal ultrasounds are done until a patient is scheduled for FET (once the endometrium reaches a thickness of ≥7mm). P4 supplementation is initiated 5 days prior to FET and serum E2 levels are measured the day prior to FET. Patients unable to achieve an endometrial thickness ≥7mm were excluded. Data was evaluated by student's t-test and multivariate binary logistic regression model.

**Results:**

A total of 1787 patients underwent single, euploid FET cycles resulting in a 60.8% implantation rate (n=1087). Estradiol administration ranged from 10 to 36 days (mean: 17.7 ± 3.2). There was no significant difference in the duration of estradiol administration (17.6 +/- 3.0, range: 11-36 days vs. 17.8 +/- 3.4, range: 10-33 days, p=0.36) or serum estradiol levels (338.9 ± 225.6 vs. 362.3 ± 273.8. p=0.07) according to whether successful implantation occurred. Controlling for age at FET, oocyte age, BMI, endometrial thickness and day of embryo biopsy, the duration of estradiol exposure and serum estradiol level achieved prior to FET did not impact the odds of implantation (OR 0.99 [95% CI 0.96-1.03], p=0.72), ongoing pregnancy (OR 0.99 [95% CI 0.96-1.02], p=0.34) or early pregnancy loss (EPL) (OR 1.02 [95% CI 0.98-1.06], p=0.26). There was a significant positive correlation between days of estradiol administration and serum estradiol levels the day before FET (r=0.06, p=0.01). With increasing serum estradiol levels, there was a trend toward reduced odds of implantation (AUC 0.58, p=0.05) and ongoing pregnancy (AUC 0.59, p=0.09) and increased EPL (AUC 0.59, p=0.08) albeit this did not reach statistical significance.

**Conclusions:**

Implantation potential was sustained regardless of the length of estradiol supplementation prior to FET. The endometrium responds uniformly to a variety of durations, delivery systems, and dosages of estradiol treatment, while maintaining receptivity. There was a trend toward supraphysiologic serum estradiol levels' exerting a negative impact on clinical outcome, though prolonged supplementation of up to 36 days prior to FET was not deleterious. The follicular phase is compliant and not limited to a specific duration of estradiol supplementation. These findings confirm that FET can be flexibly scheduled to allow coordination of clinical care (ie. delay embryo transfer until PGT results are available) without compromising clinical outcome.

**Support:**

None.