



# Luteal Estradiol Does Not Influence Outcomes in Letrozole-Induced Modified Natural Frozen Embryo Transfer Cycles

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## BACKGROUND

Letrozole is widely used to induce ovulation in modified-natural frozen embryo transfer (FET) cycles and is known to lower systemic estradiol (E2) levels. In programmed FETs, inadequate E2 has been linked to impaired endometrial receptivity, raising questions about whether similar concerns apply in letrozole cycles. Although clinicians routinely monitor follicular development and endometrial thickness, the clinical relevance of mid-luteal E2 levels in predicting implantation and pregnancy outcomes remains uncertain.

## OBJECTIVE

To determine whether luteal E2 levels impact pregnancy outcomes in letrozole-induced modified natural FET cycles.

## METHODS & MATERIAL

- **Study Design:** Multisite retrospective cohort study of letrozole-induced modified natural FET cycles of PGT-A tested embryo (April 2024 to August 2025)
- **Exclusion Criteria:** Cycles without luteal E2 levels, non-letrozole protocols or progesterone (P4) level <2ng/dL on Luteal Day (LD) 4. LD defined from ovulation; hCG trigger given on confirmed (LD-1) or expected (LH-2) surge. Progestin supplementation administered if P4 < 9 ng/dL
- **Outcomes:** Pregnancy outcomes were categorized by hCG-negative, pregnancy of unknown location (PUL), or clinical pregnancy (positive hCG with ultrasound-confirmed intrauterine pregnancy). E2 levels were measured on LD2 and 4.
- **Statistical Analysis:** Group comparisons performed using Chi-square, Fisher's exact, ANOVA or Kruskal-Wallis tests across pregnancy outcome groups

Across all measured time points, luteal-phase estradiol shows no association with pregnancy likelihood.

	HCG-negative (N=100)	Pregnancy of Unknown Location (N= 27)	Clinical Pregnancy (N=277)	P-value
Age, Mean (SD)	36.8 (3.3)	36.8 (2.8)	37.2 (3.7)	0.61
BMI, Mean (SD)	25.4 (5.6)	27.4 (6.8)	23.6 (6.1)	<0.001
Mean P4 on LD2 [ng/dL]	11.50 (5.90)	11.39 (6.42)	10.47 (5.71)	0.28
Mean P4 on LD4 [ng/dL]	25.57 (10.22)	22.72 (7.23)	25.78 (8.81)	0.28
Endometrium thickness (mm)	8.61 (1.60)	9.47 (1.57)	8.77 (1.38)	0.08
E2 on LD2 (pg/mL)				
Mean (SD)	69.20 (58.60)	89.65 (79.98)	72.16 (78.52)	
Median (IQR)	50.50 (34.60-78.05)	61.10 (41.80-105.00)	56.20 (41.30-76.70)	0.16
E2 on LD4 (pg/mL)				
Mean (SD)	103.44 (88.44)	94.68 (28.45)	83.65 (46.81)	
Median (IQR)	66.50 (47.40-128.00)	99.20 (71.70-110.50)	74.60 (47.90-103.70)	0.12

## RESULTS

- 422 letrozole-FET cycles included: 24.4% hCG-negative (100), 6.9% PUL (n=27) and 68.7% clinical pregnancies (n=277)
- Baseline characteristics were similar across pregnancy outcome groups
- BMI differed significantly (p<0.001), with the PUL group demonstrating the highest mean BMI
- Median E2 levels on LD2 and LD4 were similar across pregnancy outcomes (p=0.16, p=0.12; **Table 1**)
- Endometrial thickness was not significantly different across pregnancy outcomes (p=0.082; **Table 1**)
- P4 levels on LD2 and LD4 were also comparable across pregnancy outcomes (p=0.28, p=0.28; **Table 1**)

## FIGURE 1

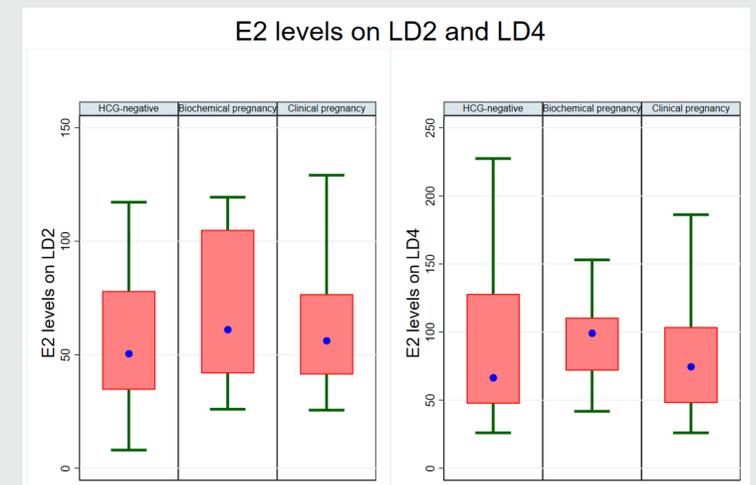


Figure 1: Box plot illustrating median and mean (blue dots) E2 levels measured on LD2 (left) and LD4 (right) across three pregnancy outcomes (hCG-negative, biochemical pregnancy and clinical pregnancy)

## DISCUSSION/CONCLUSION

Mid-luteal estradiol levels on luteal days 2 and 4 did not differ across pregnancy outcomes and were not associated with endometrial thickness. Despite the characteristically lower physiologic E2 levels in letrozole-induced cycles, endometrial development and implantation remained unaffected. These findings indicate that endogenous estrogen production provides adequate luteal support in letrozole-induced FET cycles, and routine luteal E2 monitoring or supplemental estrogen is unlikely to improve outcomes. Larger studies are warranted to confirm these findings and refine monitoring strategies while avoiding unnecessary intervention.

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