IMPACT OF THE CORPUS LUTEUM ON EARLY SERUM HCG CONCENTRATIONS FOLLOWING FROZEN EMBRYO TRANSFER

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Background
Increasing data indicates that the presence of a corpus luteum (CL) during frozen embryo transfer (FET) impacts downstream maternal outcomes such as preeclampsia. Some evidence suggests early hCG concentrations may be predictive of adverse outcomes. However, there is limited data comparing hCG patterns across different FET protocols. These include natural cycle (NC FET) and letrozole cycles (LTZ FET), where the CL is present, and hormone replacement treatment cycles (HRT FET), where the CL is absent.

Objective
Our objective was to determine whether there were differences in early hCG concentrations and patterns differ between NC, LTZ, and HRT FET cycles. Additionally, we aimed to explore potential associations between hCG concentrations with clinical characteristics.

Materials and Methods
This was a prospective study of autologous blastocyst FET (NC, LTZ, HRT) performed between 2021-2023 at a single academic center. All cycles with a positive initial hCG (ie. hCG >=5 mIU/ml) were included. LTZ FET was performed with letrozole 5mg x 5d. For NC/LTZ FET, hCG trigger was administered with lead follicle >17mm. FET was performed 7d after hCG trigger or 3d after serum P4 levels reached >=5ng/mL, per physician preference. HRT FET was performed with estradiol (oral, vaginal or patch) followed by intramuscular and vaginal progesterone. Serum hCG was generally measured 8 days post-FET and repeated 48 hours later. The following hCG patterns were analyzed: initial hCG, hCG % change, initial hCG <100 mIU/ml (low hCG), and hCG that did not double over 48 hours (hCG non-doubling). Generalized estimating equations accounted for multiple cycles per patient and adjusted for covariates. Regression and ANOVA were used to investigate associations between hCG concentrations and clinical characteristics. Sub-analyses were performed limited to cycles with ongoing pregnancies.

Results
A total of 1251 cycles among 963 patients were performed between 2021-2023. Of these, 917 had an initial positive hCG and were included in analyses. Baseline clinical characteristics are presented in Table 1. The mean initial hCG values were similar across groups (p=0.6536) (Table 2). HRT FET cycles were significantly more likely to have low hCG and hCG non-doubling on univariate analyses. This finding did not persist in adjusted models nor in sub-analyses of ongoing pregnancies. There was no significant correlation between early hCG patterns and age, AMH, gravidity, parity, endometrial thickness, follicle diameter, or peak E2. However, there was a significant correlation between initial hCG and BMI (r=-0.11, p<0.001). Similarly, there were progressively lower hCG values with higher BMI categories (p<0.0001) (Table 3). These findings persisted in sensitivity analyses limited to ongoing pregnancies.

Conclusions
Overall, our results suggest that hCG patterns are similar across different FET protocols, despite presence or absence of a CL. The most robust association between hCG patterns and clinical characteristics was noted between initial hCG and BMI. There were no associations between hCG % change or hCG non-doubling. This suggests that despite having lower initial hCG concentrations, those with higher BMI should be expected to have a similar relative change in early serial hCG concentrations.

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Table 1. Patient and cycle characteristics

	NC FET	LTZ FET	HRT FET	p-value	adj p-value*
Age at freeze	35.3 (3.7)	34.2 (3.7)	34.8 (3.7)	0.0191	0.1545
Age at transfer	36.4 (3.5)	35.2 (3.8)	36.2 (3.8)	0.0012	0.0126
BMI	24.3 (4.7)	26.4 (6.4)	27 (5.9)	<0.0001	<0.0001
AMH	3.2 (2.2)	4.8 (3.7)	4.6 (4.2)	<0.0001	0.0692
Gravidity	1.6 (1.4)	1.6 (1.8)	1.5 (1.5)	0.7358	0.7224
Parity	0.6 (0.7)	0.5 (0.7)	0.6 (0.7)	0.244	0.0882
Prior SAB	83 (45.4%)	103 (46%)	228 (44.7%)	0.896	0.9874
PGT-A	138 (75.4%)	150 (67%)	347 (68%)	0.1313	0.5121
EMT	9.4 (2.1)	8.5 (2.1)	9.4 (2.1)	<0.0001	<0.0001
Follicle diameter	19.6 (2.9)	20.3 (3.1)	---	0.0291	0.045
Peak E2	272.5 (210.3)	288.7 (415.7)	---	0.6328	0.2179
Cycle outcome					
Ongoing	147 (80.3%)	173 (77.2%)	368 (72.2%)	0.0607	0.2167
Chemical	24 (13.1%)	27 (12.1%)	88 (17.3%)	0.4159	0.7536
Ectopic	0 (0%)	3 (1.3%)	4 (0.8%)	0.483	0.4544
SAB	12 (6.6%)	21 (9.4%)	50 (9.8%)	0.1331	0.2003

Data presented as mean (SD) or count (percent). *adjusted for age, BMI, diagnosis, cycle outcome. Abbreviations: AMH, antimullerian hormone; BMI, body mass index; E2, estradiol; EMT, endometrial thickness; PGT-A, preimplantation genetic testing for aneuploidy; SAB, spontaneous abortion

Table 2. Early hCG patterns

	NC FET	LTZ FET	HRT FET	p-value	adj p-value*
Initial hCG	144.8 (204.6)	138.3 (196.9)	120.5 (189.8)	0.2606	0.6536
hCG % change	167.2 (195.7)	152.8 (89.5)	145 (227.4)	0.4436	0.9742
hCG <100	76 (41.5%)	102 (45.5%)	262 (51.4%)	0.0485	0.4601
hCG < double	33 (18%)	38 (17%)	130 (25.5%)	0.0076	0.0717
Any abnormal hCG	86 (47%)	110 (49.1%)	285 (55.9%)	0.06	0.3976

Data presented as mean (SD) or count (percent). Units hCG concentration reported in mIU/ml. *adjusted for age at freeze, BMI, diagnosis, and cycle outcome

Table 3. Initial hCG concentration among BMI categories

BMI category	hCG concentration, mean (SD)	count
<18.5	166.0 (142.7)	20
18.5 - <25	117.1 (75.5)	405
25 - <30	120.5 (136.2)	221
30 - <35	83.7 (50.2)	111
35 - <40	77.4 (46.7)	51
>=40	75.8 (44.8)	30
		839*
P-ANOVA	p<0.0001	
P-Regression	p<0.001	

Data presented as mean (SD). Units hCG concentration reported in mIU/ml. *Analysis limited to cycles where hCG was measured 8 days post-FET. P-ANOVA, p-value following Kruskal-Wallis test. P-Regression, p-value for regression slope per mid-point each category