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Title

Lack of Progesterone Rise Post-Trigger Correlates With Sub-Optimal Clinical Outcomes Despite Normal Fertilization Rate

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Objective:
A rise in serum luteinizing hormone (LH) and progesterone (P_4) after an r-hCG trigger, which mimics an endogenous LH flare, indicates oocyte maturation initiation. Previously, P_4level post-trigger has been characterized as an independent predictor of number of total oocytes and mature oocytes retrieved. This study sought to analyze clinical outcomes in patients with differing levels luteinization.

Design:
Retrospective cohort analysis

Materials and Methods:
Patients who underwent an autologous IVF cycle with a r-hCG trigger between July 2002 and July 2015 were included. Cases with a post-trigger β-hCG level <40 mIU/mL were excluded . P_4 rise post-trigger was measured and considered absent (<1 ng/mL), low (1.0 – 1.5 ng/mL), intermediate (1.6 – 2.3 ng/mL) or normal rise (>2.3 ng/mL). Levels as low as 2.3 and as high as 40.1 ng/mL have been observed within relatively short interval of time (60-90 minutes) spanning a single secretory pulse. Patients were additionally segregated according to the proportion of mature oocytes fertilized (<25%, 25-50%, 51-75% and >75%) and P_4 level was compared. Pearson correlations were used to analyze correlation between age, BMI, Day 3 FSH, AMH and total GND dosage with post-trigger P_4 levels. A binary logistic regression analysis was used to model the influence of P_4 level on pregnancy rate (PR), clinical PR, early pregnancy loss rate and live birth rate (LBR).

Results:
A total of 16087 cycles were studied. Patient's demographic, stimulation, laboratory parameters and clinical outcomes are shown in Table 1. Normal (n=10797; P_4: 4.4±2.0), intermediate rise

(n=3535; P_4: 2.0±0.3), low rise (n=1321; P_4: 1.3±0.1) and absent luteinization (n=434; P_4: 0.8±0.2) cycles were identified. Age (r= -0.17), BMI (r= -0.09), day 3 FSH (r= -0.19) and total GND dose (r= -0.23) had a negative correlation and AMH (r=0.18) had a positive correlation with the level of P_4. Fertilization rate was observed similar between <2.3 or >2.3 ng/mL: 51.7% vs. 53.6% vs. 54.2% vs. 55.8%, respectively ($p<0.05$). P_4 level was similar when compared according to the proportion of embryos fertilized (<25, 25-50, 51-75 and >75): 2.9 vs. 3.4 vs. 3.6 vs. 3.2 ng/mL, respectively. Raw data analysis showed PR (34.4% vs. 41.6% vs. 49.6% vs. 56.5%, respectively; $p<0.001$), clinical PR (26.4% vs. 32.5% vs. 39.7% vs. 46.5%, respectively; $p<0.001$), early pregnancy loss rate (16.2% vs. 17.2% vs. 18.1% vs.18.2%, respectively; NS) and LBR (17.4% vs. 23.8% vs. 30.9% vs. 38.0%, respectively; $p<0.001$) increased with increasing post-trigger P_4 level.
After adjusting for age, Day 3 FSH, AMH, BMI and total GND dose in a logistic regression model, elevated P_4 was still associated with increased odds of pregnancy (OR 1.074 (95% CI 1.056 – 1.092), $p<0.001$), clinical pregnancy (OR 1.068 (95% CI 1.051 – 1.086), $p<0.001$); and live birth (OR 1.074 (95% CI 1.057 – 1.093), $p<0.001$), with no influence on early pregnancy loss rate (OR 1.009 (95% CI 0.988 – 1.030), NS).

Conclusions:
IVF post-trigger P_4 levels independently predicted ongoing PR, clinical PR, early pregnancy loss rate and LBR outcomes. All study cohorts demonstrated adequate fertilization rates. However, luteinization was correlated with the likelihood of live birth, with a P_4 level >2.3 ng/mL, as reflected by the highest LBR in study. The level of P_4 at trigger is an accurate prognostic indicator of cycle outcome and can be used prior to oocyte retrieval to enhance patient counseling and expectations.

Support:
None.

Table:

	<1 ng/mL (n=434)	1.0 – 1.5 ng/mL (n=1321)	1.6 – 2.3 ng/Ml (n=3535)	>2.3 ng/mL (n=10797)	Absent vs. Normal	
Age (years)	39.1±4.4	38.4±4.5	37.7±4.4	36.5±4.7	p<0.0001	
Day FSH (mIU/mL)	8.1±4.9	7.4±4.2	7.0±3.9	5.9±3.3	p<0.0001	
AMH (ng/mL)	0.6±1.5	0.9±2.2	1.2±1.4	2.2±5.4	p<0.0001	
BMI	25.9±5.2	25.1±5.2	24.3±4.7	23.8±4.5	p<0.0001	
E_2 at surge (pg/mL)	934.7±606.1	1164.5±627.6	1558.9±778.4	2345.2±1033.9	p<0.0001	
P_4 at surge (ng/mL)	0.3±0.1	0.4±0.1	0.6±0.2	1.1±0.7	p<0.0001	
E_2 at +1 (pg/mL)	1174.2±776.0	1515.9±919.0	2011.9±1106.9	2959.4±1368.8	p<0.0001	
P_4 at +1 (ng/mL)	0.8±0.1	1.2±0.1	2.0±0.3	4.3±1.9	p<0.0001	
GND total (IU)	4289.2±1439.4	4201.1±1369.8	4018.3±1373.7	3472.9±1337.7	p<0.0001	

Retrieved	4.8±3.6	6.6±4.1	9.3±5.1	15.6±8.0	p<0.0001	
Day 1 ongoing	2.5±2.2	3.5±2.8	5.1±3.5	8.7±5.6	p<0.0001	
Fertilization rate	51.7% (1074/2079)	53.6% (4650/8682)	54.2% (22629/41745)	55.8% (86104/154231)	NS	
Pregnancy Rate	34.4% (142/413)	41.6% (518/1244)	49.6% (2081/4197)	56.5% (5195/9193)	p<0.001	OR 1.074 95% CI 1.056 – 1.092
Clinical PR	26.4% (109/413)	32.5% (404/1243)	39.7% (1664/4195)	46.5% (4275/9186)	p<0.001	OR 1.068 95% CI 1.051 – 1.086
Early Pregnancy Loss Rate	16.2% (67/413)	17.2% (212/1243)	18.1% (761/4195)	18.2% (1671/9186)	NS	OR 1.009 95% CI 0.988 – 1.030
Live Birth Rate	17.4% (71/409)	23.8% (293/1231)	30.9% (1286/4163)	38.0% (3477/9149)	p<0.001	OR 1.074 95% CI 1.057 – 1.093