LUTEAL PROGESTERONE TESTING IS NOT ASSOCIATED WITH IMPROVED LIVE BIRTH IN PROGRAMMED FROZEN EMBRYO TRANSFER CYCLES UTILTIZING PROGESTERONE IN OIL

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BACKGROUND

Screening for low levels of progesterone (P4) improves outcomes in programmed frozen embryo transfer (FET) cycles in the setting of exclusive vaginal P4.

Intramuscular progesterone-in-oil (PIO), either exclusively or in combination with vaginal P4, is now standard of care because it reliably achieves adequate P4 levels and optimizes FET outcomes.

The utility of measuring P4 in FET cycles utilizing intramuscular progesterone-in-oil (PIO) is unknown, and a source of significant practice variation.

OBJECTIVE

Determine if there is an association between luteal progesterone (P4) testing and live birth in programmed FET cycles utilizing PIO.

METHODS

- Retrospective analysis of programmed single euploid FET cycles utilizing PIO across a large multi-center fertility network, 2010–2023. Cycles with uterine factor as an infertility diagnosis were excluded.
- Primary outcome was live birth. Secondary outcomes included positive pregnancy test, clinical pregnancy, and miscarriage.
- Luteal P4 testing was defined as P4 testing from 2 days after initiation of exogenous P4 to 14 days after embryo transfer. Low luteal P4 defined as P4 < 10 ng/ml
- Generalized Estimating Equations (GEE) were used to fit a Poisson regression model of live birth. Patient-level observation clustering was used to account for multiple transfers per patient.

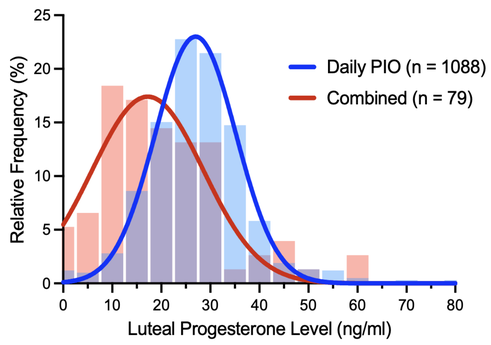
RESULTS

Characteristics of cycles with & without P4 testing

	No P4 testing (n = 17,842)	P4 testing (n = 1,170)
Age at transfer (y)	36.2 (4.4)	36.1 (4.6)
Age at retrieval (y)	34.6 (4.2)	34.6 (4.3)
BMI (kg/m2)	26 (23 - 30)	25 (22 - 30)
Donor-derived embryo	2129 (11.9%)	125 (10.7%)
Primary diagnosis		
DOR	2564 (14.4%)	199 (17.0%)
Endometriosis	514 (2.9%)	27 (2.3%)
Tubal factor	1325 (7.4%)	89 (7.6%)
Male factor	3653 (20.5%)	209 (17.9%)
Ovulatory factor	2219 (12.4%)	227 (19.4%)
Unexplained	2975 (16.7%)	146 (12.5%)
Blastulation day		
Day 5	**9775 (54.8%)**	**709 (60.6%)**
Day 6	**6381 (35.8%)**	**336 (28.7%)**
Day 7	436 (2.4%)	18 (1.5%)
P4 Regimen		
Daily PIO	**12073 (67.7%)**	**1088 (93.0%)**
Combined PIO / PV	**4751 (26.6%)**	**79 (6.8%)**

Unadjusted analysis of cycle outcomes, by P4 testing

	No P4 testing (n = 17,842)	P4 testing (n = 1,170)	
Live birth	8863 (49.7%)	603 (51.5%)	p = 0.23
Positive hCG	**12726 (71.3%)**	**868 (74.2%)**	**p = 0.04**
Clinical IUP	**10944 (61.3%)**	**755 (64.5%)**	**p = 0.03**
Miscarriage	1953 (10.9%)	126 (10.8%)	p = 0.89



Distribution of P4 levels, by regimen

Low P4 levels were rare (3.7% of all cycles), but more common with the combined regimen than daily PIO (15.2% vs. 2.9%, p < 0.0001).

There was no **significant difference in live birth** between cycles based on P4 regimen (p = 0.79), or low vs. normal measured P4 (p = 0.25).

Regional variation in P4 regimen, testing, and outcomes

Clinic	Total Cycles	Cycles with P4 testing	P4 Regimen	LBR
A	1523	604 (39.7%)	Daily PIO: 1447 (95.0%); Combined: 52 (3.4%)	44.4%
B	2441	22 (0.9%)	Daily PIO: 1957 (80.2%); Combined: 398 (16.3%)	44.7%
C	3315	72 (2.2%)	Daily PIO: 3088 (93.2%); Combined: 136 (4.1%)	50.2%
D	**324**	**275 (84.9%)**	**Daily PIO: 290 (89.5%); Combined: 5 (1.5%)**	**56.2%**
E	1202	64 (5.3%)	Daily PIO: 1066 (88.7%); Combined: 97 (8.1%)	56.5%
F	9437	122 (1.3%)	Daily PIO: 4696 (49.8%); Combined: 4109 (43.5%)	50.8%
G	727	6 (0.8%)	Daily PIO: 576 (79.2%); Combined: 33 (4.5%)	49.1%

Poisson Regression Analysis: Adjusted Risk Ratios for Cycle Outcomes

	Risk Ratio (95% CI)			
	Live birth	Positive hCG	Clinical IUP	Miscarriage
Luteal P4 testing				
No testing	Referent	Referent	Referent	Referent
Testing	0.99 (0.92 - 1.06)	1.01 (0.97 - 1.05)	1.00 (0.95 - 1.06)	0.96 (0.79 - 1.17)
Age at Transfer (y)	1.00 (0.99 - 1.00)	1.00 (1.00 - 1.00)	1.00 (0.99 - 1.00)	1.00 (0.99 - 1.01)
P4 Regimen				
Daily PIO	Referent	Referent	Referent	Referent
Combined	1.01 (0.98 - 1.04)	**1.03 (1.01 - 1.05)**	1.02 (1.00 - 1.05)	1.08 (0.98 - 1.19)
Other	0.96 (0.90 - 1.03)	0.98 (0.93 - 1.02)	0.95 (0.89 - 1.00)	0.89 (0.72 - 1.09)
Obesity status				
Non-obese	Referent	Referent	Referent	Referent
Obese	**0.86 (0.83 - 0.89)**	**0.96 (0.94 - 0.98)**	**0.94 (0.91 - 0.96)**	**1.26 (1.15 - 1.38)**
Blastulation Day				
Day 5	Referent	Referent	Referent	Referent
Day 6	**0.76 (0.74 - 0.79)**	**0.85 (0.84 - 0.87)**	**0.81 (0.79 - 0.83)**	1.04 (0.95 - 1.13)
Day 7	**0.43 (0.36 - 0.51)**	**0.60 (0.54 - 0.66)**	**0.53 (0.47 - 0.60)**	1.06 (0.81 - 1.37)
Clinic site				
Site D	**1.14 (1.02 - 1.28)**	**1.07 (1.00 - 1.15)**	**1.13 (1.03 - 1.23)**	1.16 (0.82 - 1.63)
All other sites	Referent	Referent	Referent	Referent

CONCLUSIONS

- Adjusting for clinic site, age, P4 regimen, obesity, and blastulation day, **there was no association between luteal P4 testing and chance of live birth** in programmed FET cycles utilizing intramuscular PIO.
- **Testing for luteal P4 levels is not associated with improved FET outcomes** and may be **unnecessary when intramuscular PIO is used**, either daily or in combination with vaginal progesterone.

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