CHARACTERISTICS OF FRESH EMBRYO TRANSFERS AND ECTOPIC PREGNANCY RISK: ASSOCIATION BETWEEN ELEVATED PROGESTERONE AND ECTOPIC PREGNANCY

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SGF shady grove fertility

INTRODUCTION

- Ectopic pregnancies are more likely to occur following fresh embryo transfers (ETs)[1]
- Biologic studies suggest estradiol (E2) and progesterone (P4) can alter tubal function, uterine contractility and endometrial receptivity to an ET at time of trigger [2-4]
- Elevated serum E2 and P4 at time of trigger have been linked with EP following all ET[5-7]
- More data is needed to understand roles of E2, P4 and endometrial thickness (EMT) and risk of EP following fresh ET

OBJECTIVE

Evaluate association and risk of EP after a fresh ET with serum levels of E2 and P4, and EMT on day of trigger.

MATERIALS AND METHODS

- Retrospective chart review of a multicenter private practice between 2009-2023
- Inclusion: age 19-45 years, fresh autologous ET
- Exclusion: smokers, tubal disease, history of prior EP, heterotopic or c-section scar EP
- Adjusted for age, BMI, clinic site, parity, race, ethnicity, number of cycles, primary infertility diagnosis
- Non-parametric tests used for baseline characteristics
- Generalized linear mixed models used to account for cycle repeats with modified Poisson regression for cycle outcomes
- Linear trend and spline analyses used to evaluate non-linear associations and determine categorical hormone thresholds for cycle outcomes
- Combined stratified analysis used to evaluate multi-hormone association on EP risk

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RESULTS

	Ectopic, heterotopic (n=169)[1]	No ectopic, no heterotopic [2] (n=23327)[1]	p-value[3]
Age (mean ± SD)	33.0 ± 3.5	33.6 ± 4.1	0.13
Race/Ethnicity			0.3
White	11 (6.5%)	2082 (8.9%)	
Black	11 (6.5%)	2017 (8.7%)	
Hispanic/Latinx	7 (4.1%)	1107 (4.8%)	
Asian	35 (20.7%)	3494 (15.0%)	
American Indian/ Alaskan Native	0 (0.0%)	30 (0.1%)	
Multiple/Other	0 (0.0%)	37 (0.2%)	
Unknown	7 (4.1%)	786 (3.4%)	
BMI (mean ± SD)	27.0 ± 5.7	26.1 ± 5.7	0.05
Primary diagnosis (n, %)			
Diminished ovarian reserve	15 (8.9%)	2672 (11.5%)	
Endometriosis	8 (4.7%)	1074 (4.6%)	
Male infertility	50 (29.6%)	7152 (30.7%)	
Ovulation disorders/PCO	30 (17.8%)	3840 (16.5%)	
Uterine factor	2 (1.2%)	461 (2.0%)	
Other	11 (6.5%)	1867 (8.0%)	
Unexplained	50 (29.6%)	5608 (24.0%)	
Not entered	3 (1.8%)	653 (2.8%)	
Cycle Outcome			
Biochemical	0 (0.0%)	1873 (8.0%)	
Clinical intrauterine gestation	0 (0.0%)	11662 (50.0%)	
Ectopic	165 (97.6%)	0 (0.0%)	
Heterotopic	4 (2.4%)	0 (0.0%)	
Not entered	0 (0.0%)	5 (0.0%)	
Not pregnant	0 (0.0%)	9785 (42%)	
Unknown	0 (0.0%)	2 (0.0%)	
E2 (mean ± SD), pg/mL	2947.5 ± 1267.7	2652.5 ± 1290.2	**0.002**
P4 (mean ± SD), ng/mL, *missing 4683*	1.2 ± 0.5	1.1 ± 0.5	**<0.001**
EMT (mean ± SD), mm, *missing 265*	10.8 ± 2.4	11.5 ± 2.6	**<0.001**

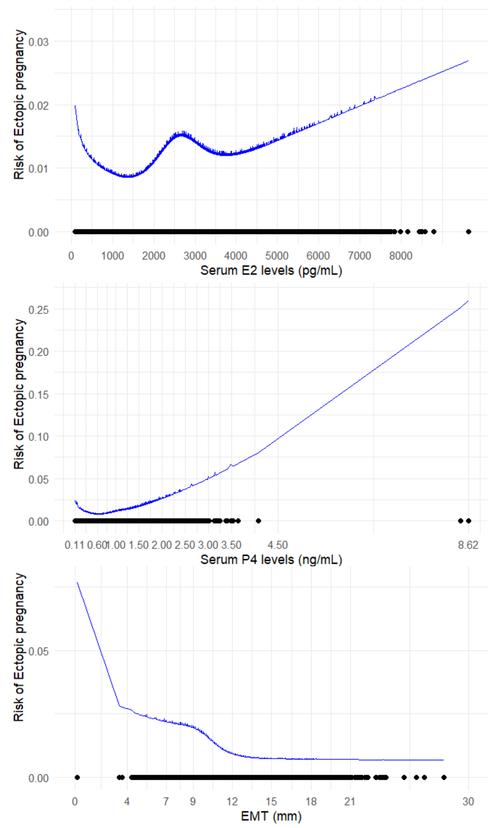
Table 1. Selected cycle characteristics and outcomes after fresh ET.

[1] n (%), [2] Includes biochemical, clinical pregnancy, not pregnant; Wilcoxon rank sum test, [3]Fisher's exact test; Pearson's Chi-squared test

Characteristic (mean, min, max)	Ectopic, heterotopic	Intrauterine pregnancy	Biochemical	Not pregnant	p-value*
E2	2434.3 (2251.0, 2632.7) †	2242.4 (2194, 2291.7)	2253.2 (2186.9, 2321.4)	2091.9 (2046.8, 2138.1) †	**<0.001**
P4	1.1 (1.0, 1.3)	1.0 (0.9, 1.0)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	**<0.001**
AFC	11.2 (10.1, 12.3)	12.3 (12.0, 12.7)	12.1 (11.6, 12.5)	11.1 (10.8, 11.4)	**<0.001**
FSH	5.7 (5.2, 6.3)	6.1 (5.9, 6.2)	6.1 (5.9, 6.4)	6.1 (6.0, 6.3)	0.38
E2/P4 ratio	2.3 (2.1, 2.6)	2.5 (2.4, 2.7)	2.4 (2.2, 2.6)	2.3 (2.1, 2.4)	**<0.001**
EMT	10.6 (10.3, 11.0)	11.5 (11.4, 11.6)	11.2 (11.1, 11.4)	11.1 (11, 11.2)	**<0.001**

Table 2. Mean hormone levels and EMT by cycle outcome.
Adjusted for female age, BMI, clinic site, parity, race/ethnicity, number of cycles, primary infertility diagnosis.
E2, P4 and EMT values representative of day of trigger serum levels.
*Corrected by Tukey's adjustment; †Significant difference compared to EP outcome

RISK OF EP AND SERUM E2, P4, AND EMT



RESULTS

- Across 23,503 fresh autologous ET cycles from 20,967 patients, 0.70% were EP, with significant differences in mean E2, P4 and EMT values.
- Risk of EP was increased with E2 > 2000 pg/mL (aRR 1.61, CI 1.11 - 2.34), P4 > 1ng/mL (aRR 1.95, CI 1.37-2.77). Risk of EP was decreased with EMT > 9mm (aRR 0.5, CI 0.35-0.72).
- When stratified by E2 > 2000 or < 2000 pg/mL, associations between EP and P4 remained significant (aRR 1.78, CI 1.18 – 2.70) and (aRR 2.18, CI 1.05-4.50).
- When E2 > 2000 pg/mL, associations between EP and EMT remained significant (aRR 0.46, CI 0.31-0.68).
- When stratified by P4 > 1ng/mL and < 1 ng/mL, the association between elevated E2 and EP risk was no longer seen (aRR 1.19, CI 0.67-2.11) and (aRR 1.4, CI 0.77-2.57).

CONCLUSIONS

EP after fresh ET is linked to higher serum E2 and P4 and thinner EMT at time of trigger. Combined stratified analysis suggests that P4 is the main driver of EP in fresh ET. Consider delineating threshold values for serum E2, P4 levels and EMT to decrease risk of EP following fresh ET.