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Title:

SUPRAPHYSIOLOGIC LEVELS OF STEROID HORMONES DURING FROZEN EMBRYO TRANSFER CYCLES ARE NOT ASSOCIATED WITH ECTOPIC PREGNANCY RISK

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Objective:

The underlying mechanism for an ectopic pregnancy (EP) following an intrauterine embryo transfer is not fully understood. While ectopic pregnancies result from alterations in the tubal environment in most natural cycles, endometrial receptivity is the primary concern following in vitro fertilization (IVF). Elevations in estradiol and progesterone levels during controlled ovarian stimulation (COS) are associated with morphological changes in the endometrium that may augment or interfere with normal implantation. Perhaps as a result of the exaggerated hormonal environment resulting from IVF stimulation, the risk of EP has been shown to be greater during a fresh compared to frozen embryo transfer (ET) cycle. However, despite lower steroid hormone levels in a frozen ET cycle, ectopic risk is still higher than in natural cycles. This study aimed to determine whether estradiol (E2) and progesterone (P4) levels during a frozen, blastocyst ET cycles are associated with EP risk.

Design:

Retrospective cohort study

Materials and Methods:

The study included patients who underwent IVF cycle(s) followed by a frozen, blastocyst ET between 2002 and 2018. Oocyte donation cycles were excluded from analysis. Trophectoderm biopsy and pre-implantation genetic testing for aneuploidy (PGT-A) were performed on select embryos. Patient age, body mass index (BMI), gravidity, parity, endometrial type and thickness at time of transfer, blastocyst morphologic grade, and day of embryo biopsy for PGT-A were recorded. EP was defined as a pregnancy outside of the uterus that was treated medically (with methotrexate) or surgically. Cycles were separated into groups based on pregnancy outcome (EP vs. no EP). Data were analyzed using a Student's t-test, Chi square/Fisher's Exact test, and multivariate logistic regression.

Results:

A total of 4163 patients underwent 5968 frozen, blastocyst ETs, of which 236 cycles resulted in EP (3.9%). Patients who had an FET resulting in EP had a higher BMI compared to those without an EP (24.7 ± 5.2, p=0.02). Patients in both groups were similar in age, gravidity, and parity. All patients had comparable endometrial thickness and pattern at the time of transfer, as well as similar blastocyst morphologic grades of embryos transferred (table 1). The peak E2 and P4 levels were comparable in study cohorts and not significantly associated with an EP outcome, before and after adjusting for confounders.

Conclusions:

No association between steroid hormone levels and EP risk were observed in frozen, blastocyst ET cycles. While supraphysiologic concentrations of E2 and P4 may alter endometrial gene expression and may elevate EP rate in fresh ART cycles, this association is not found in cycles using synthetic preparation for frozen embryo transfers. However, given the increased EP rate in FET cycles, as compared to the general population, other mechanisms may be at play, including embryo transfer technique, altered immune modulation of the uterine environment, and inflammatory response. Successful intrauterine implantation requires the occurrence of several precise events, including apposition, attachment and invasion of the blastocyst into the endometrium. Variations in patient hormone levels may cause specific structural and molecular changes in the luminal epithelia prior to embryo attachment that impair this process. With the use of big data and precision medicine, it is hopeful that protocols can be identified that minimize extra-uterine implantation risk by optimizing endometrial receptivity.

Support:

None.

Table 1:

Patient Demographics and Cycle Characteristics

	Ectopic (n=5732)	No Ectopic (n=236)	P Value
Age (y)	35.7 ± 3.9	35.8 ± 4.2	0.92
BMI (kg/m^2)	24.7 ± 5.2	24.0 ± 4.6	0.02
Gravidity			
- 0	67 (30.4%)	1736 (32.8%)	
- 1	61 (27.7%)	1673 (31.6%)	0.16
- 2	55 (25.0%)	1009 (19.1%)	
- ≥3	37 (16.8%)	872 (16.5%)	
Parity			
- 0	133 (61.0%)	3054 (57.8%)	
- 1	61 (28.0%)	1690 (32.0%)	0.39
- 2	21 (9.6%)	421 (8.0%)	
- ≥3	3 (1.4%)	123 (2.3%)	
Estradiol at time of Transfer	379 ± 318	348 ± 271	0.12
Progesterone at time of Transfer	24.6 ± 17.2	24.0 ± 13.8	0.68
Endometrial Thickness at time of Transfer (mm)	9.7 ± 2.0	9.7 ± 2.3	0.66
Endometrial Type at time of transfer			
- Type 2	24 (10.2%)	763 (13.4%)	0.15
- Type 3	212 (89.8%)	4939 (86.6%)	
Embryo Expansion Grade			
- 4	115 (48.7%)	2571 (45.0%)	0.09
- 5	48 (20.3%)	1530 (26.8%)	
- 6	73 (30.9%)	1614 (28.2%)	
Embryo Inner Cell Mass Grade			
- A	145 (63.9%)	3778 (68.7%)	0.43
- B	69 (30.4%)	1460 (26.6%)	
- C	13 (5.7%)	253 (4.6%)	
- D	0 (0%)	6 (0.11%)	

Embryo Trophectoderm Grade - A - B - C - D	 88 (38.8%) 104 (45.8%) 35 (15.4%) 0 (0%)	 2220 (40.4%) 2256 (41.1%) 992 (18.1%) 28 (0.51%)	 0.34
%PGT-A	143 (60.6%)	3411 (59.5%)	0.74
Day of Embryo Transfer - Day 5 - Day 6 - Day 7	 113 (47.9%) 119 (50.4%) 4 (1.7%)	 2737 (47.9%) 2887 (50.5%) 94 (1.6%)	 0.99