TITLE: THE ASSOCIATION BETWEEN ESTRADIOL LEVELS ON DAY OF TRIGGER AND LIVE BIRTH RATES IN LETROZOLE STIMULATED FROZEN EMBRYO CYCLES

AUTHORS: Arielle S. Yeshua MD[1,2], Kerry S.J. Flannagan PhD[3], Anita Pershad MD[1,2], Phillip A. Romanski, MD[4], Benjamin S. Harris MD, MPH,[1,2]

AFFILIATIONS:

1. Shady Grove Fertility – Jones Institute, 601 Colley Ave, Norfolk, VA, 23507
2. Macon and Joan Brock Virginia Health Sciences at Old Dominion University, Department of Obstetrics and Gynecology, 601 Fairfax Avenue, Norfolk, VA 23507
3. Shady Grove Fertility - Rockville, 9601 Blackwell Road, Rockville, MD, 20850
4. RMA of New York, 635 Madison Avenue, New York, NY, 10022

BACKGROUND: Prior research evaluating letrozole for ovulation induction has shown that estradiol levels below the 25th percentile in intrauterine insemination cycles are associated with poorer outcomes (1). The degree of estradiol suppression by letrozole varies among patients, and the impact of these reduced estradiol levels on endometrial preparation during frozen embryo transfer warrant further investigation.

OBJECTIVE: To evaluate live birth relative to estradiol level on the day of trigger in Letrozole stimulated frozen embryo transfer (FET) cycles.

MATERIALS AND METHODS: We performed a retrospective cohort study of all patients in a private fertility network who underwent autologous single blastocyst letrozole-stimulated FET cycles from January 2017 to November 2023. Patients with a diagnosis of recurrent pregnancy loss, unmitigated uterine factor, use of gestational carriers or donor gametes were excluded. Cycles using gonadotropins and/or estradiol supplementation to increase endometrial thickness were also excluded. Estradiol (E2) levels were divided into three distinct categories: (1) "Low E2", defined as <10th percentile (<91.9 pg/mL) E2 serum level on the day of ovulation trigger; (2) "Normal E2", defined as between the 10th and 90th percentiles and (3) "High E2", defined as > 90th percentile (>352 pg/mL). Risk ratios and 95% confidence intervals were calculated to evaluate live birth among the defined estradiol level categories using Poisson regression models fitted with generalized estimating equations. Outcomes were adjusted for age, BMI and PGT-A use.

RESULTS: A total of 968 cycles were included in the analysis. Median E2 level at trigger was 75 pg/mL, 184.9 pg/mL and 505.4 pg/mL for the <10th percentile group, 10-90th percentile group and >90th percentile group respectively. Endometrial thickness did not differ significantly between the three groups. Live birth occurred in 47.5% of cycles with estradiol in the 10th-90th percentile, which was not significantly different from the <10th% group (38.5%; RR 0.82 (0.62-1.1)) or the >90th% group (38.0% (RR 0.79 (0.57-1.06)). Clinical pregnancy loss occurred in 7.5% of cycles with estradiol in the 10th-90th percentile, which was not significantly different from the <10th% group (7.1%; RR 0.9 (0.33-2.43)) or the >90th% group (5.2% 0.76 (0.24-2.36)) (Table 1).

CONCLUSIONS: Peak E2 levels at time of trigger in letrozole stimulated frozen embryo transfer cycles, falling below the 10th percentile or exceeding the 90th percentile were not associated with a decreased live birth rate compared to cycles in which E2 levels fell within the 10-90th percentile range. Although these results did not achieve statistical significance, this may be due to the limited sample sizes in the cohorts characterized by particularly low or high estradiol levels.

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REFERENCES:

1. Live birth associated with peak serum estradiol levels in letrozole intrauterine insemination cycles. New, Erika P. et al. Fertility and Sterility, Volume 119, Issue 5, 785 - 791

Table 1. Cycle Outcomes by Estradiol Levels in Letrozole-Stimulated Frozen Embryo Transfer Cycles

	<10th Percentile (<91.9)		10th-90th Percentile (91.9-352.3)		>90th Percentile (>352.3)		
	N (%)	RR (95% CI)	N (%)	RR (95% CI)	N (%)	RR (95% CI)	P, trend
Biochemical pregnancy rate*	3 (5.2)	0.45 (0.14, 1.42)	57 (10.4)	Ref	5 (8.2)	0.88 (0.37, 2.11)	0.29
Clinical pregnancy rate	51 (53.7)	0.84 (0.69, 1.02)	489 (64.8)	Ref	55 (57.9)	0.87 (0.73, 1.04)	0.79
Live birth rate	30 (38.5)	0.82 (0.62, 1.1)	280 (47.5)	Ref	27 (38)	0.78 (0.57, 1.06)	0.82
Preterm Delivery**	5 (16.7)	0.75 (0.33, 1.71)	58 (20.7)	Ref	5 (18.5)	0.92 (0.4, 2.13)	0.68
Intrauterine fetal demise*	0 (0)	NA	4 (0.9)	Ref	1 (1.9)	1.97 (0.25, 15.52)	0.21
Ectopic pregnancy*	4 (6.9)	7.34 (1.9, 28.38)	5 (0.9)	Ref	1 (1.6)	1.98 (0.26, 15.13)	0.08
Clinical pregnancy loss*	4 (7.1)	0.9 (0.33, 2.43)	39 (7.5)	Ref	3 (5.2)	0.76 (0.24, 2.36)	0.84

*losses calculated out of pregnancies
**preterm births calculated out of live births