

TITLE: PRE-TRIGGER ESTRADIOL (E2) DYNAMICS: A NON-GENOMIC EVALUATION OF EMBRYO QUALITY

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BACKGROUND: Physicians monitor the rising E2 level in relation to follicular growth during in vitro fertilization (IVF) cycles. A drop in E2 level prompts concern regarding possible attrition of follicles or initiation of ovulation prior to trigger injection.

OBJECTIVE: The study aimed to evaluate the association between change in E2 levels over the 24-hour period leading up to trigger injection.

MATERIALS & METHODS: The study included IVF cycles from September 2016 - December 2022. All cycles included vaginal oocyte retrieval (VOR), intracytoplasmic sperm injection (ICSI) and plan to freeze embryos after biopsy and screen by preimplantation genetic testing for aneuploidy (PGT-A). Cycles were grouped by the change in E2 from the day prior to trigger to the day of trigger injection: Group 1: increase in E2 >10%, Group 2: plateau of E2 (between -10% to +10%), Group 3: decrease in E2 >10%. Patient and cycle characteristics including age, AMH, BMI, BAFC, trigger day, estradiol level on day of trigger, change in E2 over 24-hours, number of oocytes retrieved and rates of oocyte maturation, fertilization, blastulation, and euploidy were collected. Comparative analysis was performed using Kruskal-Wallis. Multivariate logistic regression fitted with generalized estimating equation was performed to compare maturity, fertilization, blastulation, and euploidy rates between groups.

RESULTS: A total of 9,421 cycles met inclusion criteria – Group 1: 8373, Group 2: 973, Group 3: 77 cycles. The mean maturation rate was similar between the groups (1: 76.1%, 2: 75.8%, 3: 76.3%, $p=0.838$). Logistic regression adjusted for age, AMH, BMI, trigger day, E2 level, change in E2, and number of oocytes and mature oocytes retrieved showed significantly lower odds of fertilization (OR 0.66 CI 0.48-0.90 $p = 0.009$) and blastulation (OR 0.75 CI 0.58-0.98 $p = 0.036$) in patients with a drop in E2 >10% as compared to an increase in E2 on the day of trigger. Cycles with a plateau in E2 had similar odds of fertilization (OR 1.08 CI 0.98-1.12 $p=0.14$) and blastulation (OR 1.07 CI 0.97-1.17 $p = 0.18$) compared to those with an increase in E2. Euploidy rates showed no difference between groups on unadjusted analysis (45.8% vs 43.2% vs 43.9%, $p = 0.073$) and showed similar odds of euploidy on adjusted model.

CONCLUSIONS: Despite similar oocyte maturity rates, cycles with a drop >10% in E2 from the day before trigger to the day of trigger had significantly lower fertilization and blastulation rates compared to cycles with a plateau or increase in E2 levels. A drop in E2 may be an indicator of reduced embryonic developmental competence. Physicians can be reassured that a plateau in E2 does not portend poor oocyte quality, as shown by similar fertilization and blastulation rates. Furthermore, the change in E2 is not associated with ploidy status of embryos reaching the blastocyst stage. This information can be used to counsel patients regarding potential IVF outcome, given their response to ovarian stimulation.

	Group 1 (n = 8373)	Group 2 (n = 971)	Group 3 (n = 77)	p
Maturation Rate	76.20%	75.80%	76.30%	0.838
Fertilization Rate	78.60%	78.60%	70.30%	0.038
Group 3 v 1	OR 0.66, CI 0.48 - 0.90			0.0091
Group 2 v 1	OR 1.01, CI 0.98 - 1.19			0.138
Group 2 v 3	OR 1.65, CI 1.20-2.26			0.002
Blastulation Rate	43.40%	41.60%	35.20%	0.002
Group 3 v 1	OR 0.75, CI 0.58 - 0.98			0.036
Group 2 v 1	OR 1.07, CI 0.97 - 1.18			0.176
Group 2 v 3	OR 1.42, CI 1.09 - 1.85			0.011
Euploidy Rate	45.8%	43.2%	43.9%	0.073