



AMERICAN SOCIETY FOR
REPRODUCTIVE MEDICINE



77th ASRM Scientific Congress & Expo
October 16-20, 2021 // Baltimore, MD, USA

PATIENTS WHO REQUIRE SUPRA-PHYSIOLOGIC ESTROGEN SUPPLEMENTATION TO ACHIEVE ADEQUATE ENDOMETRIAL THICKNESS FOR EUPLOID EMBRYO TRANSFERS ARE AT INCREASED RISK OF PRETERM DELIVERY AND LOWER BIRTH WEIGHT

Devora Aharon, MD¹, Kelsey Martin, MD¹, Dmitry Gounko, MA², William J Hanley, BA², Joseph A. Lee, BA², Daniel E. Stein, MD¹, Alan B Copperman, MD² and Rachel S. Gerber, MD³

1. Icahn School of Medicine at Mount Sinai, New York, NY
2. Reproductive Medicine Associates of New York, New York, NY, (3)Icahn School of Medicine at Mount Sinai

OBJECTIVE:

Supra-physiologic estradiol (E2) levels are associated with decreased live birth rates in frozen embryo transfer cycles, possibly due to an underlying endometrial defect requiring additional supplementation.¹ This study aims to determine whether patients with elevated serum E2 levels during single euploid frozen-thawed embryo transfer (FET) are at increased risk for neonatal morbidity including preterm birth and low birth weight.

MATERIALS AND METHODS:

This retrospective cohort study included all synthetic single euploid FET from September 2016-August 2020. Patients with serum E2 ≥ 600 pg/mL were compared to those with E2 < 600 pg/mL at the time of progesterone start. Gestational age (GA) at delivery, preterm birth (PTB) rate (< 37 weeks, < 34 weeks, and < 28 weeks), birth weight (BW), and rate of low birth weight (LBW, < 2500 g), very low birth weight (VLBW, < 1500 g) and macrosomia (> 4000 g) were compared between the groups. Student's t-test, chi-square test, and multiple linear and logistic regression were used for analysis.

RESULTS:

Out of 6033 FET cycles, 5215 patients had E2 < 600 (86.4%) and 818 had E2 ≥ 600 (13.6%). Live birth rate (≥ 24 weeks GA) was 49.8% among patients with E2 < 600 (N=2596) and 40.6% among patients with E2 ≥ 600 (N=332) ($p < .0001$). E2 ≥ 600 was significantly associated with lower gestational age at delivery (38.7 ± 2.1 vs. 39.0 ± 1.9 , $p = .005$) and increased preterm birth rate < 37 weeks (14.2% vs. 9.7%, $p = .01$). PTB < 34 weeks and < 28 weeks GA were similar between the groups (3.3% vs. 2.2%, $p = .19$; 0.3% vs. 0.5%, $p = .57$). E2 ≥ 600 was significantly associated with lower BW (3190 ± 543 vs. 3327 ± 566 , $p < .0001$), higher rates of LBW (10.8% vs. 7.5%, $p = .046$) and lower rates of macrosomia (4.4% vs. 8.5%, $p = .02$). No difference was seen in VLBW (0.7% vs. 0.9%, $p = .70$). Multiple linear regression controlling for age, BMI, AMH, endometrial thickness, and uterine factor diagnosis demonstrated that E2 ≥ 600 was associated with significantly lower GA at delivery ($\beta = -0.33$, 95% CI -0.55- -0.10, $p = .004$) and lower birth weight ($\beta = -120$, 95% CI -190- -51, $p = .0007$). Logistic regression adjusting for the variables above showed significantly elevated odds of PTB < 37 weeks (OR 1.60, 95% CI 1.14-2.26, $p = .007$) as well as low birth weight (OR 1.56, 95% CI 1.04-2.35, $p = .03$). When adjusting for GA as well, a significant impact of elevated E2 on LBW and macrosomia was no longer seen, but a significantly lower birth weight overall persisted ($\beta = -55$, 95% CI -108- -3, $p = .04$).

CONCLUSIONS:

Patients with supra-physiologic serum estradiol levels in synthetic single euploid FET cycles are at increased risk for preterm birth and lower birth weight. This association may reflect underlying



AMERICAN SOCIETY FOR
REPRODUCTIVE MEDICINE



endometrial dysfunction leading to increased estrogen requirement to achieve an optimal endometrial thickness.

IMPACT STATEMENT:

Patients who require high doses and alternate routes of estrogen to achieve adequate thickness in FET cycles appear to be at risk for neonatal morbidity, despite ultimately reaching a sufficient thickness. This supports a relationship between the process of developing the endometrial lining and subsequent fetal growth and gestation.

REFERENCES:

1. Fritz R, Jindal S, Feil H, Buyuk E. Elevated serum estradiol levels in artificial autologous frozen embryo transfer cycles negatively impact ongoing pregnancy and live birth rates. *J Assist Reprod Genet.* 2017 Dec;34(12):1633-1638. doi: 10.1007/s10815-017-1016-1. Epub 2017 Aug 19. PMID: 28823065; PMCID: PMC5714815.