EFFECT OF ESTRADIOL SUPPLEMENTATION ON PREGNANCY OUTCOMES IN PATIENTS WITH THIN ENDOMETRIAL LINING UNDERGOING INTRAUTERINE INSEMINATION

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Background: Adequate endometrial lining development plays a crucial part in embryo implantation. Given that estradiol drives endometrial lining development and that endometrial thickness (EMT) is thought to impact pregnancy outcomes, it stands to reason that estradiol supplementation may help improve outcomes by increasing EMT. Thus far, the utility of estrogen supplementation in intrauterine insemination (IUI) cycles with thin EMT remains largely unstudied.

Objective: To study the effect of estradiol supplementation in the follicular/proliferative phase of IUI cycles on endometrial thickness and pregnancy outcomes.

Materials and Methods: The study included all patients who completed an IUI cycle at a single university-affiliated fertility center from 2017-2023. Cycles that received estradiol supplementation were compared to a reference cohort of cycles with no supplementation. The reference cohort was categorized into cycles with pre-ovulatory EMT <7mm ("thin-lining") and ≥7mm ("normal-lining"). Patients in the estradiol cohort started vaginal micronized estradiol (Estrace, 2mg tablets twice a day) in the proliferative phase if EMT was <5 or 6mm (depending on follicular size) when the dominant follicle was >15mm; this was continued until they were confirmed to either have a negative pregnancy test or viable intrauterine pregnancy. The primary outcome was the change in EMT prior to IUI. The secondary outcomes were rates of positive pregnancy test, clinical pregnancy, clinical miscarriage, and live birth. Generalized estimating equation method for multivariable logistic regression was performed to account for the correlation between cycles per patient.

Results: A total of 2,281 cycles were included in analysis: 309 cycles with estradiol supplementation and 1,972 reference cycles without supplementation (536 cycles had thin-lining [<7mm] and 1436 had normal-lining [≥7mm]). The estradiol cohort was older than the unsupplemented reference cohort (mean age 38 compared to 37 years, p=0.001). The two cohorts had similar BMI, median total motile sperm count, and number of IUI cycles completed. The estradiol cohort underwent greater proportions of medicated IUI compared to more natural IUI cycles in the reference cohort. When compared with the thin-lining reference cohort, estradiol supplementation led to a significantly greater change in EMT from baseline to ovulation trigger (2.4cm vs 1.9cm, P=<0.0001, Table 1). Similar rates of positive pregnancy test, clinical pregnancy and live birth between the estradiol cohort and the two reference groups were observed (Table 2). After adjusting for age, BMI, race, infertility diagnosis, and EMT at trigger, the estradiol cohort

had a statistically significant increased odds of clinical miscarriage compared to the entire reference cohort (adjusted OR 2.05, 95% confidence interval [1.13, 3.71], p=0.02, Table 2); this increased rate of miscarriage was only observed in clomiphene IUI cycles upon subanalysis stratifying by medicated IUI type.

Conclusion: Estradiol supplementation in the proliferative phase statistically significantly increased EMT from baseline to ovulation trigger compared to IUI cycles with unsupplemented thin pre-ovulatory EMT (<7mm). However, this change did not translate into improved IUI outcomes such as increased rates of clinical pregnancy and live birth or decreased rate of miscarriage.

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Table 1: Endometrial thicknesses (EMT, mm) among IUI cycles with and without exogenous estradiol (E2). Data presented as mean(standard deviation).

	Estradiol N = 309	No Estradiol Thin lining (<7mm) N = 536	No Estradiol Normal lining (≥7mm) N = 1436		E2 vs. no E2 (<7mm) p-value	E2 vs. no E2 (≥7mm) p-value
EMT at baseline scan	4.2 (3.3, 5.0)	4.6 (3.6, 5.6)	4.8 (3.9, 6.1)		**0.001**	**<0.0001**
EMT at trigger	6.6 (5.8, 7.5)	6.4 (6.0, 6.7)	8.4 (7.7, 9.6)		**<0.0001**	**<0.0001**
Change in EMT from baseline to trigger	2.4 (1.3, 3.7)	1.9 (1.0, 2.9)	3.8 (2.5, 4.9)		**<0.0001**	**<0.0001**

Table 2. Pregnancy outcomes of IUI cycles with and without exogenous estradiol (E2). Data presented as n(%).

	Estradiol	No Estradiol Thin Lining (<7mm)	No Estradiol Normal lining (≥7mm)		E2 vs. no E2 (<7mm) p-value	E2 vs. no E2 (≥7mm) p-value
Positive β-hCG	44 (16.2)	75 (16.2)	214 (16.4)		0.98	0.94
Clinical pregnancy	39 (14.4)	64 (13.8)	199 (15.3)		0.41	0.35
Clinical miscarriage	18 (40.1)	23 (30.7)	56 (26.2)		0.34	0.10
Live birth	21 (7.8)	40 (8.6)	139 (10.7)		0.68	0.15

	aOR (95% CI)[a]	p-value
Clinical Pregnancy	1.17 (0.79, 1.75)	0.43
Clinical Miscarriage	2.05 (1.13, 3.71)	**0.02**
Live birth	0.85 (0.50, 1.45)	0.56

[a]aOR = adjusted odds ratio. Covariates include maternal age, BMI, race, infertility diagnosis, and EMT at trigger