

DIFFERENTIAL ENDOMETRIAL RESPONSIVENESS TO ENDOGENOUS VS EXOGENOUS ESTROGEN EXPOSURE DOES NOT PREDICT LIVE BIRTH

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Background

Optimizing the endometrial cavity for embryo implantation remains a key goal in assisted reproductive technology. Transvaginal sonographic measurement of endometrial thickness (EMT) is commonly used as a minimally invasive, cost-effective proxy for endometrial receptivity during frozen embryo transfer (FET) cycles, and low peak EMT has been associated with decreased live birth (1,2). It is unknown whether reproductive outcomes differ between patients who develop a thin endometrium in response to both gonadotropins during ovarian stimulation and exogenous estrogen during the subsequent FET cycle, when compared to patients who develop a robust endometrium in response to gonadotropins but who respond poorly to exogenous estrogen. As no interventions reliably improve pregnancy outcomes in the setting of a thin endometrium, this information may help identify patients who would benefit from FET cycle cancelation and another attempt at endometrial preparation, and patients for whom such management may not be beneficial.

Objective

The study evaluated the association between endometrial response to exogenous estrogen exposure (FET-EMT) and live birth, and whether this association is modified by data from the endometrial response to endogenous estrogen produced during gonadotropin stimulation (IVF-EMT).

Materials and Methods

This retrospective cohort study evaluated 31,828 patients who underwent FET after an autologous IVF cycle at a large network of fertility clinics between January 2017 and July 2024. The first IVF cycle and first subsequent FET cycle were included for analysis. Cases of uterine factor infertility were excluded. The primary outcome was live birth, with secondary outcomes of clinical pregnancy and pregnancy loss. Modified Poisson regression models were used to estimate risk ratios (RR) for each outcome. Patients were stratified by IVF-EMT to test whether the relationship between IVF-EMT and FET-EMT was associated with cycle outcomes.

Results

Nulliparity and ovulatory dysfunction were more prevalent among patients with a thin (<7mm) FET-EMT. Controlling for age, BMI, race/ethnicity, AMH, use of PGT, number of embryos transferred, and cycle protocol used, every 1 mm increase in IVF-EMT was associated with a 2% (RR: 1.02; 95% CI: 1.01, 1.02) increase in live birth. A similar association was observed between FET-EMT and live birth (RR: 1.02; 95% CI 1.01, 1.03). In a stratified analysis, there was no association between increasing FET-EMT and pregnancy outcome among patients who

had a thin (<7mm) IVF-EMT. For patients with an IVF-EMT ≥ 7 mm, increasing FET-EMT was associated with marginally increased live birth (RR 1.05; 95% CI 1.02, 1.08).

Conclusions

Increased EMT, whether due to endogenous estrogen production during gonadotropin stimulation or exogenous estrogen exposure during an FET cycle, is associated with a modest increase in live birth. The difference in endometrial response to endogenous versus exogenous estrogen is also associated with live birth, however the magnitude of this effect is small, and is not seen in the critical group of patients who do not develop robust endometrial proliferation at the time of IVF. These findings suggest that cycle cancelation and protocol changes to improve endometrial proliferation are unlikely to improve outcomes among patients who develop a thin lining in response to gonadotropin stimulation.

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References:

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Table 1: Stratified Analysis of Pregnancy Outcomes

| | Total | FET-EMT | P | P, interaction |
|-------------------------|--------------|----------------------|--------|----------------|
| Pregnancy Outcome | N (%) | RR per 1 mm (95% CI) | | |
| IVF-EMT <7mm | | | | |
| Live Birth | 170 (42) | 1.08 (0.97, 1.19) | 0.16 | 0.006 |
| Clinical Pregnancy | 216 (53.3) | 1.04 (0.94, 1.14) | 0.45 | 0.08 |
| Chemical Pregnancy | 262 (64.7) | 1.03 (0.94, 1.12) | 0.55 | 0.20 |
| Pregnancy Loss | 86 (32.8) | 0.89 (0.75, 1.05) | 0.15 | 0.002 |
| IVF-EMT 7-10mm | | | | |
| Live Birth | 3231 (48.7) | 1.05 (1.02, 1.08) | 0.0007 | |
| Clinical Pregnancy | 3943 (59.4) | 1.03 (1.01, 1.06) | 0.02 | |
| Chemical Pregnancy | 4631 (69.7) | 1.02 (1, 1.04) | 0.12 | |
| Pregnancy Loss | 1312 (28.3) | 0.92 (0.88, 0.96) | 0.0004 | |
| IVF-EMT >10mm | | | | |
| Live Birth | 11044 (52) | 1.01 (1, 1.02) | 0.01 | |
| Clinical Pregnancy | 13530 (63.7) | 1.01 (1, 1.02) | 0.02 | |

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|-----------------------|--------------|----------------|------|--|
| Chemical Pregnancy | 15492 (72.9) | 1.01 (1, 1.01) | 0.19 | |
| Pregnancy Loss | 4246 (27.4) | 0.98 (0.97, 1) | 0.04 | |