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Use of Tamoxifen Citrate with Hormone Replacement Therapy in Frozen Embryo Transfer Cycles for Thin Endometrium: A Retrospective Study

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ABSTRACT

Background: Thin endometrium remains a significant limiting factor in Assisted Reproductive Technology (ART), Particularly in Frozen Embryo Transfer (FET) cycles, where optimal endometrial receptivity is crucial for implantation.

Objective: To evaluate the efficacy of Tamoxifen citrate in combination with Hormone Replacement Therapy (HRT) in improving Endometrial Thickness (EMT) and reproductive outcomes in patients with refractory thin endometrium.

Methods: This retrospective study included 126 patients with EMT <7 mm despite conventional therapies. Patients received Tamoxifen (40 mg/day, Days 2–6) along with estradiol valerate. EMT before and after treatment and biochemical pregnancy rates were analyzed.

Results: A statistically significant increase in EMT was observed (6.51 ± 0.75 mm vs 7.64 ± 0.59 mm; $p < 0.001$). The biochemical pregnancy rate was 69%.

Conclusion: Tamoxifen in combination with HRT significantly enhances endometrial thickness and improves reproductive outcomes in refractory thin endometrium.

INTRODUCTION

Successful embryo implantation in ART depends on a synchronized interaction between embryo quality and endometrial receptivity. While advances in embryology have significantly improved embryo quality, optimization of the endometrial environment continues to remain a challenge in a subset of patients.

Endometrial thickness (EMT), assessed via transvaginal ultrasonography, is one of the most widely used surrogate markers of endometrial receptivity. Numerous studies have demonstrated that an EMT of ≥7 mm is associated with improved implantation and pregnancy rates, whereas thinner endometrium is linked to suboptimal outcomes, including implantation failure and increased cycle cancellations [1,2].

Thin endometrium is relatively uncommon but clinically significant. It may result from a variety of etiologies, including prior uterine instrumentation, infections such as genital tuberculosis, intrauterine adhesions, diminished endometrial vascularity, or altered hormonal responsiveness [3–5]. These factors may impair the proliferative capacity of the endometrium and disrupt its receptivity.

Despite multiple therapeutic interventions, management remains challenging. Conventional strategies such as high-dose estrogen therapy, extended estrogen administration, vaginal sildenafil, intrauterine G-CSF infusion, and PRP therapy have shown variable success rates [6–8]. Furthermore, these treatments are often associated with increased cost, invasiveness, and inconsistent outcomes.

Tamoxifen citrate, a Selective Estrogen Receptor Modulator (SERM), has emerged as a promising alternative. It exerts estrogen-like effects on the endometrium, promoting proliferation and enhancing vascularity while maintaining a favorable safety profile when used short term [9,10]. In contrast to exogenous estrogen therapy, Tamoxifen may improve endogenous hormonal responsiveness, making it particularly useful in resistant cases.

Recent literature suggests that Tamoxifen-based protocols in FET cycles may lead to improved EMT, reduced treatment duration, and better reproductive outcomes compared to conventional HRT [11,12]. However, data specifically focusing on refractory thin endometrium remain limited.

This study aims to evaluate the effectiveness of Tamoxifen combined with HRT in improving endometrial thickness and pregnancy outcomes in patients with refractory thin endometrium.

MATERIALS AND METHODS

Study design: Retrospective study between 2020-2024. No. of patients 126

Inclusion criteria: Age 23–45 years

Documented EMT < 7 mm on Day 17/18 (luteal phase)

History of poor endometrial response in prior FET cycles

Exclusion criteria: Age < 23 or > 45 years

History of tuberculosis, endometriosis, uterine anomalies, or Tamoxifen allergy

Protocol: All patients underwent ovarian stimulation and embryo freezing. As the initial EMT was < 7mm in luteal phase, patients underwent hysteroscopic metroplasty. In frozen embryo transfer cycles, they received hormone replacement therapy with estradiol valerate 4mg twice a day starting from Day 2 of the cycle. They also received Granulocyte Colony stimulating factor (GCSF) injections 2 doses on day 14 and day 16 and underwent Platelet rich plasma (PRP) treatment but as the EMT was still < 7mm, the cycle was cancelled. Intervention: In the Next Cycle, Tamoxifen citrate 40 mg/day from Day 2–6 and estradiol valerate (4mg BD) was started from Day 3 for 14 days. Monitoring of EMT from Day 14 onward. Clinical outcomes such as cycle continuation and implantation rates were analysed.

Table 1: Descriptive Statistics Continuous Variables (n=126)

Study Variables	Mean ± SD	Median (IQR)	Range (Min – Max)
Age	36.52 ± 5.13	36.00 (33.00, 40.00)	22.00 (27.00 – 49.00)
Endometrium thickness On Estrogen only	6.51 ± 0.75	6.70 (6.20, 7.00)	5.40 (2.00, 7.40)
Endometrium Thickness on Tamoxifen and estrogen	7.64 ± 0.59	7.70 (7.20, 8.00)	3.20 (6.20, 9.40)

SD: Standard Deviation; IQR: Interquartile Range; Min: Minimum; Max: Maximum

Table 2: Descriptive Statistics Categorical Variables (n=126)

Study Variables	Numbers (n)	Percentage (%)
Plan		
ED	14	11.1
OD	43	34.1
FET	31	24.6
OPU-DS	3	2.4
OPU-SS	35	27.8
Hysteroscopy		
Yes	126	100.0
No	0	0.0
Embryo Transfer Count		
SET	25	19.8
DET	101	80.2
Day of Embryo		
Day-5	95	75.4

Day-6	31	24.6
Embryo-I Grade		
Grade-I	123	97.6
Grade-II	3	2.4
Embryo-II Grade (n=101)		
Grade-I	95	94.1
Grade-II	6	5.9

n: Numbers; %: Percentage

Table 3: Comparison of Endometrium Before Tamoxifen vs Endometrium After Tamoxifen (n=126)

Variable	Statistics	Before Tamoxifen	After Tamoxifen	p value
Endometrium	Mean ± SD	6.51 ± 0.75	7.64 ± 0.59	**<0.001***
	95% CI (Mean)	(6.38, 6.64)	(7.53, 7.74)	
	Median (IQR)	6.70 (6.20, 7.00)	7.70 (7.20, 8.00)	

*: Wilcoxon Signed Ranks Test; SD: Standard Deviation; IQR: Interquartile Range; %: Percentage

Table 4: Biochemical Pregnancy Rate (n=126)

Variable	Calculation	Percentage (%)
Biochemical Pregnancy Rate	87/126	69.0%

n: Numbers; %: Percentage

Statistical Methods

Descriptive statistics were used to summarize both continuous and categorical variables. For continuous variables such as age and endometrial thickness, the mean ± standard deviation (SD), median with interquartile range (IQR), and range (minimum–maximum) were reported to capture central tendency and dispersion.

Categorical variables including treatment plans, hysteroscopy status, embryo transfer count, embryo day, and embryo grading were summarized using frequency counts (n) and percentages (%).

To compare endometrial thickness before and after Tamoxifen treatment, the Wilcoxon Signed Ranks Test was employed due to the paired nature of the data and potential non-normal distribution. Results were presented as mean ± SD, 95% confidence intervals (CI) for the mean, and median (IQR). A p-value < 0.05 was considered statistically significant.

The biochemical pregnancy rate was calculated as a proportion of pregnancies to total sample size and expressed as a percentage.

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA).

Thin endometrium continues to represent one of the most difficult clinical scenarios in reproductive medicine. Despite technological advances in ART, achieving optimal endometrial receptivity remains a limiting factor for successful implantation in a subset of patients.

1. Understanding Endometrial Receptivity Beyond Thickness

Although EMT is widely used as a clinical marker, endometrial receptivity is a multifactorial process involving hormonal signaling, immune modulation, angiogenesis, and molecular interactions between the embryo and endometrium. Recent research has highlighted the role of cytokines, integrins, and gene expression profiles in determining receptivity [13].

However, EMT remains a practical and non-invasive parameter in routine clinical practice. In this context, improving EMT to an acceptable threshold remains a key therapeutic goal.

2. Pathophysiological Basis of Refractory Thin Endometrium

Patients with refractory thin endometrium often exhibit reduced responsiveness to estrogen, possibly due to:

- Altered estrogen receptor expression
- Chronic endometrial damage
- Reduced uterine blood flow
- Stromal fibrosis

These factors result in impaired proliferation and suboptimal preparation of the endometrium for implantation [3,5].

3. Mechanistic Insights into Tamoxifen Action

Tamoxifen acts through selective modulation of estrogen receptors, demonstrating tissue-specific effects. In the endometrium, it functions predominantly as an estrogen agonist, leading to enhanced cellular proliferation and stromal expansion.

Additionally, Tamoxifen has been shown to:

- Increase endometrial vascularity via angiogenic pathways
- Improve uterine blood flow
- Upregulate growth factors such as VEGF
- Enhance stromal–epithelial interaction

These combined effects contribute to improved endometrial development and receptivity [9,10].

Another important aspect is its ability to stimulate endogenous hormonal pathways, which may be particularly beneficial in patients who fail to respond to exogenous estrogen therapy.

The findings of this study are consistent with recent literature. Ji et al. (2023) reported a significant improvement in EMT and live birth rates with Tamoxifen use in FET cycles [11]. Similarly, Shi et al. (2023) demonstrated improved endometrial parameters and comparable pregnancy outcomes with Tamoxifen

combined with HRT [12]. The magnitude of EMT improvement observed in this study (~1.1 mm increase) aligns with these reports, reinforcing the reproducibility of Tamoxifen's effect. Crossing the threshold of 7 mm is clinically significant, as implantation rates increase substantially beyond this level. Studies have consistently shown poor outcomes in patients with EMT <6 mm, whereas those achieving ≥7 mm demonstrate significantly improved pregnancy rates [1,2].

In this study, Tamoxifen facilitated this transition in a majority of patients, thereby enhancing their chances of successful implantation.

- Advantages of Tamoxifen Protocol
- Compared to other therapies, Tamoxifen offers several practical advantages:
- Oral administration
- Cost-effectiveness
- Short duration of treatment
- Good patient compliance
- Minimal invasiveness

These factors make it particularly suitable in resource-limited settings.

Role as Rescue Therapy

A notable strength of this study is its focus on patients who had previously failed multiple therapeutic modalities. The favorable response observed suggests that Tamoxifen may serve as an effective rescue therapy in refractory cases.

Its mechanism of action, distinct from conventional therapies, may allow it to overcome resistance and improve outcomes in otherwise difficult-to-treat patients.

Impact on Pregnancy Outcomes

The biochemical pregnancy rate of 69% observed in this study is encouraging and suggests improved endometrial receptivity. While biochemical pregnancy is an early indicator, it reflects successful implantation and provides a basis for further evaluation in terms of clinical pregnancy and live birth rates.

Safety Considerations

Short-term use of Tamoxifen in ART cycles appears to be safe. Although long-term use has been associated with endometrial pathology, recent evidence suggests that short-duration therapy does not significantly increase risk [14,15].

No major adverse effects were observed in this study.

CONCLUSION

Tamoxifen citrate, when combined with hormone replacement therapy, represents a promising therapeutic option for patients with refractory thin endometrium. It significantly improves endometrial thickness and enhances implantation potential, offering a practical and cost-effective solution in FET cycles.

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