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The Effect of Tamoxifen on Thin Endometrium in Patients Undergoing Frozen–Thawed Embryo Transfer

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Abstract

Tamoxifen has played a vital role in endocrine therapy for the treatment of estrogen receptor–positive breast cancer. We examined the effect of tamoxifen in patients with a thin endometrium in frozen–thawed embryo transfer (FET) cycles and compared the improvement in endometrial thickness (EMT) and pregnancy outcomes stratified by different etiologies of thin endometrium. A total of 226 women were recruited for a new tamoxifen protocol; all had an EMT of less than 7.5 mm in previous cycles, including natural cycle (NC), hormone replacement treatment (HRT), and ovulation induction (OI) cycles. Compared with previous cycles, tamoxifen cycles showed a significantly increased EMT (from 6.11 $\pm$ 0.98 mm to 7.87 $\pm$ 1.48 mm in the NC group, from 6.24 $\pm$ 1.01 mm to 8.22 $\pm$ 1.67 mm in the HRT group, and from 6.34 $\pm$ 1.03 mm to 8.05 $\pm$ 1.58 mm in the OI group; all $P < .001$). Patients were further divided into 3 groups based on the causes of their thin endometrium: (1) history of intrauterine adhesion (n = 34), (2) history of uterine curettage (n = 141), and (3) polycystic ovary syndrome (PCOS; n = 51). Patients with PCOS obtained the thickest EMT (9.31 $\pm$ 1.55 mm), the lowest cycle cancellation rate (11.76%), and the highest rate of clinical pregnancy (60%) and live birth (55.56%) per transfer ($P < .001$). Multivariable regression analysis showed that EMT was related to live birth (odds ratio: 1.487; 95% confidence interval: 1.172-1.887). A tamoxifen protocol improves EMT in patients after NC, HRT, and OI cycles during FET. Patients with PCOS show the most benefit from tamoxifen and achieve better pregnancy outcomes.

Keywords

tamoxifen, thin endometrium, frozen–thawed embryo transfer, intrauterine adhesion, PCOS

Introduction

Successful implantation depends on favorable uterus receptivity,[1] as evaluated by endometrial thickness (EMT), (sub)endometrial blood flow, and the endometrial pattern.[2] Of these factors, EMT is particularly important given the association of thin endometrium with poor pregnancy outcomes in assisted reproductive technology (ART) treatment.[3] Multiple protocols have been proposed to increase the thickness of thin endometrium in frozen–thawed embryo transfer (FET) cycles. These protocols include hormonal replacement with estrogen[4]; intrauterine infusion of granulocyte colony-stimulating factor,[5] endometrial somatic stem cells, or bone marrow mesenchymal stem cells[6]; and other protocols using aspirin,[7] vitamin E plus pentoxifylline,[8,9] L-arginine, or sildenafil.[10] However, all the protocols showed controversy and none of them is standardized. Meanwhile, the known causes for thin endometrium are varied, such as repeated uterine curettage (UC), chronic pelvic inflammation, endocrine factors, and idiopathic thin endometrium. Methods to increase EMT suitable for different causes remain to be explored.

As a selective estrogen receptor (ER) modulator, tamoxifen exerts an antiestrogenic effect on breast tissue[11] and exerts estrogenic effects on bone mineral density, lipid profile, and the lower genital tract. The long-term use of tamoxifen in patients with breast cancer resulted in endometrial proliferation, including hyperplasia, polyps, carcinoma, and sarcoma.[12] The role of tamoxifen in ART has also been explored in recent

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years. Tamoxifen increased EMT during ovulation induction (OI), thus yielding low miscarriage rates and high live birth rates.[11,13-15] Subsequently, patients with thin endometrium were reported to achieve improved embryo implantation after tamoxifen treatment in limited FET cycles.[16,17] At present, however, larger cohort studies aiming to elucidate the effect of tamoxifen on endometrial preparation have not been reported, and the efficacy of tamoxifen for different causes of thin endometrium remains elusive. The purpose of this study is to explore the effect of tamoxifen on thin endometrium in FET cycles and compare the pregnancy outcomes in patients stratified by different causes of thin endometrium.

Materials and Methods

Participants

A total of 226 patients with thin endometrium undergoing FET from Reproductive Hospital Affiliated to Shandong University were enrolled between January 2012 and August 2015. The diagnosis of thin endometrium was EMT less than 7.5 mm on the day of ovulation or after 12 to 16 days of estradiol (E2) replacement (4-6 mg/d, Progynova; Bayer, Leverkusen, Germany). Other recruitment criteria included (1) age younger than 40 years and basic serum level of follicle-stimulating hormone <10 IU/L; (2) at least 2 previous cycles with thin endometrium, natural cycle (NC), hormone replacement treatment (HRT) with estrogen, or OI; and (3) at least 1 good quality blastocyst available for transfer. Those patients with uterine malformations, uterine myoma, endometrial polyps, genital tuberculosis, or hydrosalpinx were excluded.

A total of 226 patients were further divided into 3 groups on the basis of different causes: (1) history of intrauterine adhesion (IUA) diagnosed by hysteroscopy (n = 34), (2) history of UC (n = 141); and (3) polycystic ovary syndrome (PCOS, n = 51). To diagnose PCOS, we used modified Rotterdam criteria[18,19]: menstrual abnormalities (irregular uterine bleeding, oligomenorrhea, or amenorrhea) combined with either hyperandrogenism or polycystic ovaries, as validated in Chinese population. Written informed consent was obtained from each participant. The study procedures were approved by the institutional review board (IRB) of Center for Reproductive Medicine of Shandong University (IRB reference number 1653).

Protocols for Endometrium Preparation

Previous FET cycles. Natural cycles were recommended for patients with regular menstruation and normal ovulation. Follicle development was monitored by ultrasonography since day 10 of menstrual cycle until ovulation occurs. For patients with PCOS or anovulation, hormone replacement was suggested with 4 to 6 mg oral E2 valerate (Progynova; Bayer) daily started on day 3 and continued for 10 days. Then endometrial growth was monitored and serum levels of luteinizing hormone, E2, and progesterone were measured. The dose of subsequent E2 valerate was adjusted according to the EMT, and the maximum dose was 8 mg/d. In OI cycles, 75 IU/d of human menopausal gonadotropin (HMG; Le Baode, Livzon, Guangzhou, China) was injected from day 5; ultrasonography was performed and the dose of HMG was adjusted according to the size of follicles; 2 mg oral E2 valerate was added if the endometrium was thinner than 5 mm. When dominant follicle reached 18 mm in diameter, 6000 IU human chorionic gonadotropin (HCG; Livzon) was injected to induce ovulation. Patients with EMT less than 7.5 mm were suggested to cancel the cycle and proceed to new FET cycles.

When EMT reached 7.5 mm, luteal support would be initiated and FET was scheduled after 5 days for good blastocyst stage embryo. According to the embryo morphology assessment by the Istanbul consensus workshop, blastocysts on day 5 with inner cell mass in the hatching stage and trophectoderm layer in grade 1 to 2 were considered good embryos. Dydrogesterone (Duphaston; Abbott Biologicals B.V, Olst, the Netherlands) was orally administered until the 12th week of pregnancy.

Tamoxifen cycles. Patients were orally administered with 20 mg tamoxifen (tamoxifen citrate tablets; Health, Jinan, China) daily for 5 days since day 3 of menstrual cycle, accompanying with 1 mg/d of intravaginal 17β-E2 (E2 tablets in Femoston; Abbott Biologicals B.V) or 2 mg/d of oral E2 valerate on day 5 until the day of ovulation. Human menopausal gonadotropin was given starting on day 8 up to the spontaneous ovulation or HCG injection, and its dosage was adjusted with the development of follicles. When EMT was $\geq$7.5 mm, progestin was prescribed, and then embryo transfer and luteal support were performed using the aforementioned method.

Measurement of EMT

Endometrial thickness on ovulation day of NC, OI, and tamoxifen cycles or last day of HRT were set as the main outcomes in this study. Three observers performed the endometrial measurements according to the same criteria. Endometrial thickness was measured at the thickest part in the plane of central longitudinal axis of uterus. The measurements were repeated at least 3 times, and the mean value was recorded for analysis.

Pregnancy Outcomes

The rates of cycle cancellation, clinical pregnancy, and live birth per cycle were followed up as secondary outcomes. Cycle cancellation criterion was EMT less than 7.5 mm. Clinical pregnancy was diagnosed by observation of gestational sac on transvaginal ultrasound scan in 5 to 7 weeks after transfer. Live birth was defined as the delivery of at least 1 live-born infant after 28 weeks' gestation.

Statistical Analysis

Statistical Package for Social Science (SPSS), version 23.0 (IBM Corp, Armonk, New York) was used for data analysis.

Table 1. Basic Characteristics of Patients With Thin Endometrium.

Characteristics	Value
Age, years[a]	32.00 (28.75-36.00)
BMI[a]	22.92 (20.78-25.92)
Duration of infertility[a]	3 (2-5)
Nulliparity, n(%)[a]	40 (17.70)
Basal FSH, IU/L[b]	6.40 ± 1.65
Basal LH, IU/L[a]	5.14 (3.72-6.95)
Basal E2, pg/L[a]	35.80 (26.8-48.30)
Basal T, ng/dL[a]	26.23 (16.76-40.08)
Causes of infertility, n(%)	
Pelvic/tubal factor[c]	189 (78.65)
Endometriosis[c]	15 (9.74)
Male factor[c]	10 (4.42)
PCOS[c]	56 (24.78)
Unexplained[c]	3 (1.32)
Risks for thin endometrium, n (%)	
IUA[c]	34 (15.04)
UC[c]	141 (62.39)
PCOS[c]	51 (18.94)

Abbreviations: BMI, body mass index; E2, estradiol; FSH, follicle-stimulating hormone; IUA, intrauterine adhesion; LH, luteinizing hormone; PCOS, polycystic ovary syndrome; SD, standard deviation; T, testosterone; UC, uterine curettage

[a]Data are expressed as median (interquartile range) for continuous variables not normally distributed.

[b]Data are expressed as mean ± SD for continuous variables following normal distribution.

[c]Data are expressed as numbers (percentage) for categorical variables.

The 2-tailed value of $P < .05$ was considered statistical significant. Continuous variables following normal distribution were given as mean ± standard deviation (SD) and compared by student *t* test; continuous variables following nonnormal distribution were given as median (interquartile range) and compared by Mann-Whitney *U* test. Categorical variables were presented as count and percentage and were analyzed by χ^2 or Fisher exact test. Groups were evaluated with 1-way analysis of variance or analysis of covariance. *P* value was corrected according to Bonferroni adjustment when making multiple comparisons among groups. Multivariable logistic regression analysis was performed to identify potential factors contributing to live birth.

Results

The basic characteristics of the 226 participants are shown in Table 1. Five patients with both Asherman syndrome and PCOS were allocated to the IUA group.

Of the 226 participants, 154 patients underwent NC, 199 patients underwent HRT, and 161 patients underwent OI in previous cycles: these patients were designated as the NC, HRT, and OI groups, respectively (Table 2). Compared with the previous treatments, the new tamoxifen protocol improved EMT significantly: from 6.11 ± 0.98 mm to 7.87 ± 1.48 mm in the NC group, from 6.24 ± 1.01 mm to 8.22 ± 1.67 mm in the HRT group, and from 6.34 ± 1.03 mm to 8.05 ± 1.58 mm in the OI group (all $P < .001$).

Table 2. The Comparison of Endometrium Thickness Between Previous Cycles and Tamoxifen Cycles.

	n	EMT in Previous Cycles,[a] mm	EMT in Tamoxifen Cycles,[a] mm	*P* Value
NC group	154	6.11 ± 0.98	7.87 ± 1.48	<.001
HRT group	199	6.24 ± 1.01	8.22 ± 1.67	<.001
OI group	161	6.34 ± 1.03	8.05 ± 1.58	<.001

Abbreviations: EMT, endometrial thickness; HRT, hormone replacement treatment; NC, natural cycle; OI, ovulation induction.

[a]The EMT measured on the ovulation day of NC, OI, or tamoxifen cycles and the last day of HRT.

The baseline characteristics of patients stratified by different causes of thin endometrium are shown in Table 3. No significant differences were observed in body mass index, but the PCOS group was younger than the other 2 groups (29.02 ± 3.96 years vs 31.88 ± 5.08 years for the IUA group and 33.32 ± 4.80 years for the UC group, $P < .001$). The level of basal serum testosterone in the PCOS group was higher (45.85 ± 19.72 ng/dL vs 29.68 ± 19.53 ng/dL in the IUA group and 25.42 ± 16.06 ng/dL in the UC group, $P < .001$). The PCOS group were observed to reach the thickest endometria in tamoxifen cycles (9.31 ± 1.55 mm vs 7.29 ± 1.14 mm in the IUA group and 8.06 ± 1.55 mm in the UC group, $P < .001$). The significant difference in EMT was also observed among the 3 groups after adjustment for age. The lowest rate of cycle cancellation for thin endometrium was also found in the PCOS group (11.76% vs 47.06% in the IUA group and 28.37% in the UC group, $P < .001$).

For cycles with EMT sufficient for implantation, the PCOS group had the highest EMT (9.49 ± 1.37 mm vs 8.02 ± 0.58 mm in the IUA group vs 8.63 ± 1.08 mm in the UC group, $P < .001$). Clinical pregnancy rates (33.33% in IUA, 38.61% in UC, and 60.00% in PCOS, $P = .035$) and live birth rates (27.78% in IUA, 31.68% in UC, and 55.56% in PCOS, $P = .025$) per cycle were also significantly different among the 3 groups, with the PCOS group demonstrating better pregnancy outcomes. Multivariable logistic regression analysis showed that age and EMT were associated with live birth. The odds ratio for live birth was 0.872 for age (95% confidence interval [CI], 0.806-0.943) and 1.487 for EMT (95% CI, 1.172-1.887).

Discussion

The present study revealed that application of tamoxifen during FET increased the EMT in patients with thin endometria, compared with their previous NC, HRT, or OI cycles. The tamoxifen protocol is particularly beneficial for patients with PCOS and resulted in an improved pregnancy outcome.

A sufficient EMT is indispensable for successful pregnancy during ART. At present, the minimal EMT to support a pregnancy is controversial, with opinions ranging from 6 to 8 mm.[20,21] Noteworthy, the meta-analysis performed by Kasius et al[22] demonstrated that receiver operating characteristic (ROC) curve cannot determine a definite cutoff value for EMT

Table 3. The Comparison of Basic Characteristics, EMT, and Pregnancy Outcomes After Tamoxifen Treatment Among 3 Groups Stratified by Different Causes.

	IUA Group	UC Group	PCOS Group	*P* Value
n	34	141	51	
Age, years	31.88 ± 5.08[a]	33.32 ± 4.80[a]	29.02 ± 3.96	<.001
Nulliparity, n/N (%)	6/34 (17.65)[a]	0/141 (0)[a]	34/51 (66.67%)	<.001
BMI, kg/m^2	23.88 ± 3.79	23.32 ± 3.66	23.99 ± 3.49	NS
Basal LH, IU/L	4.25 (3.28-5.93)[a]	5.17 (3.81-6.72)[a]	6.77 (4.68-14.57)	<.001
Basal T, ng/dL	29.68 ± 19.53[a]	25.42 ± 16.06[a]	45.85 ± 19.72	<.001
EMT in tamoxifen cycles,[b] mm	7.29 ± 1.14[a]	8.06 ± 1.55[a]	9.31 ± 1.55	<.001[c]
Cycle cancellation rate, n/N(%)	16/34 (47.06)[a]	40/141 (28.37)[a]	6/51 (11.76)	<.001
EMT in cancelled cycles,[d] mm	6.50 ± 1.15	6.66 ± 1.21	6.80 ± 0.45	.845
EMT in transfer cycles,[e] mm	8.02 ± 0.58[a]	8.63 ± 1.08[a]	9.49 ± 1.37	<.001
No. of transferred embryos	1.22 ± 0.42	1.37 ± 0.50	1.55 ± 0.54	.021
Clinical pregnancy rate, n/N (%)	6/18 (33.33)	39/101 (38.61)[a]	27/45 (60.00)	.035
Live birth rate, n/N (%)	5/18 (27.78)	32/101 (31.68)[a]	25/45 (55.56)	.015

Abbreviations: BMI, body mass index; EMT, endometrial thickness; IUA, intrauterine adhesion; LH, luteinizing hormone; PCOS, polycystic ovarian syndrome; T, testosterone; UC, uterine curettage.

[a]Significant differences were found compared with the PCOS group (Bonferroni-corrected *P* value of .017 [3 tests in total] was set as the threshold).

[b]The EMT on ovulation day of each tamoxifen cycle.

[c]Significant difference was found among the 3 groups by applying analysis of covariance (adjusted for age).

[d]The EMT on ovulation day of each cancelled cycle.

[e]The EMT on ovulation day of each transfer cycle (EMT ≥7.5 mm).

to predict a successful pregnancy (areas under the ROC: 0.56), although a trend toward decreased pregnancy rate is observed in women with thin endometrium. Therefore, we used a cutoff of 7.5 mm to diagnose thin endometrium.

Tamoxifen was first used in 3 patients with unresponsive recurrent thin endometrium in 2013 and resulted in conception.[16] Subsequently, a retrospective study consisting of 61 patients with thin endometria undergoing FET showed that tamoxifen alone increased the average EMT from 6.5 to 8.8 mm.[17] Consistent with previous data, our results demonstrated that administration of tamoxifen combined with estrogen and HMG, rather than tamoxifen alone, increased EMT in the early follicular phase.

Previous studies have demonstrated that exposure to tamoxifen promotes endometrial proliferation in patients with breast cancer.[23,24] The possible mechanism may be explained by estrogen pathway and nonestrogen pathway. In the estrogen pathway, tamoxifen may activate ER and modulate the signal transduction pathways of estrogen-responsive genes.[25] Activation of G protein–coupled ER 1, which can trigger human epidermal growth factor receptor/mitogen-activated protein kinase, is essential for tamoxifen-stimulated endometrial growth.[26] Tamoxifen also contributes to local estrogen biosynthesis and estrogen metabolism,[27] which might explain that the combination of tamoxifen and estrogen resulted in improved EMT. Moreover, tamoxifen may affect the transcriptional activity of ERα and regulate the expression of ERα in endometrium, thereby promoting estrogen-mediated cell growth.[28-30] In the nonestrogen pathway, tamoxifen may promote endometrial proliferation directly both in vitro[31] and in vivo.[32] Multiple proliferation markers, such as Rb-retinoblastoma family proteins, cyclin protein, and cyclin-dependent kinase 2, were observed to increase after tamoxifen injection in mice.[33] In tamoxifen users with benign endometrial lesions, the expression of key proliferation marker Ki67, as well as apoptosis/anti-apoptosis markers Fas, FasL, and Bcl2, also elevated.[34] In addition, it has been reported that tamoxifen could stimulate epithelial proliferation of endometrium by promoting the invasion and paracrine factors released by endometrial stromal cells.[35]

According to our results, tamoxifen increased EMT in the 3 groups, with the greatest result in patients with PCOS. Consistent with the changes in EMT, patients with PCOS achieved the lowest cycle cancellation rate and highest rates of clinical pregnancy and live birth. Multivariable logistic analysis indicated that a thicker endometrium in the PCOS group contributed to a higher live birth rate, regardless of the younger age. The endocrine and metabolic disturbance in patients with PCOS may negatively affect the endometrium receptivity.[36,37] Endometrial thickness in PCOS exhibited a significant negative correlation with the serum total testosterone.[38,39] Recently, it has been shown that the level of ERα and ERα/ERβ were decreased in proliferative endometrium, whereas the level of androgen receptor was increased.[40] Therefore, the thin uterine lining in PCOS may result from changes in steroid hormones and receptors. Tamoxifen improves EMT and pregnancy outcomes in PCOS mainly through the ER pathway. In addition, fewer previous mechanical lesions to the endometrium may induce a synergetic effect and result in a better response to tamoxifen in the PCOS group.

Repeated UC led to injury to and chronic inflammation of the endometrium.[41] The functional impairment or mechanical damage is responsible for decreased endometrial regenerative activities and increased implantation failure. Our study showed that endometrium with mild to moderate damage treated with tamoxifen achieved satisfactory pregnancy outcomes. The

presence of IUA normally resulted from repeated intrauterine operations or severe pelvic infections. With the stroma largely replaced by avascular fibrous tissue, IUA represents severe damage in endometrium and is characterized by atrophic and inert endometrial lining.[42] The IUA group using tamoxifen presented the slightest improvement in EMT among the 3 etiology groups. Taking into account the histopathological features and this group's unresponsiveness to hormone stimulation, the limited observed effect of tamoxifen may be achieved through estrogen-independent pathway.

Our study does have some limitations. First, it was a retrospective and observational cohort study. Second, given that we administered tamoxifen in combination with estrogen or HMG in the new treatment protocol, elucidating the role of tamoxifen per se might be elusive. Considering that all the patients had experienced at least 2 cycles of ineffective endometrial preparation, including estrogen replacement and OI with HMG and estrogen before tamoxifen treatment, the unique role of tamoxifen in the early stage of endometrial growth should not be ignored.

In conclusion, the results of this study allow us to propose an effective and convenient tamoxifen protocol for patients with a thin endometrium undergoing FET cycles. Patients with PCOS achieved thicker endometria and better pregnancy outcomes than patients with IUA and a history of UC.

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Declaration of Conflicting Interests

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