Original Article

Tamoxifen is Better than Low-Dose Clomiphene or Gonadotropins in Women with Thin Endometrium (<7 mm) after Clomiphene in Intrauterine Insemination Cycles: A Prospective Study

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Abstract

Aim: Gonadotropin stimulation is used as the second line of treatment in patients with thin endometrium following clomiphene citrate (CC) administration, which is associated with higher cost, multiple births, and ovarian hyperstimulation syndrome. Tamoxifen (TMX), a selective estrogen receptor modulator, acts as an agonist on the endometrium. The objective of the present study was to compare the efficacy of low-dose CC, TMX, and gonadotropins in women with thin endometrium (<7 mm) following Clomiphene in intrauterine insemination (IUI) cycles. **Settings and Design:** A prospective observational study between December 2011 and June 2013 was carried out in a tertiary infertility center. **Methods:** Women (n = 502) undergoing IUI with endometrium <7 mm after 100 mg CC were included in the study and divided into three treatment groups. Women in Group A (n = 182, cycles = 364) received clomiphene (50 mg/day from day 3 to 7), Group B (n = 179, cycles = 342) received TMX (40 mg/day from day 3 to 7), and Group C (n = 141, cycles = 226) received continuous urine-derived follicle-stimulating hormone 75–150 IU from day 3 onward until human chorionic gonadotropin injection. Endometrial thickness (ET), pregnancy rate, and live birth rate were considered as main outcome measures. **Statistical Analysis:** Multiple comparisons using one-way ANOVA and Schiff's test were performed. **Results:** Pregnancy and live birth rate were significantly higher (P < 0.004) in TMX and gonadotropin groups compared to clomiphene. A number of follicles in the TMX group were found to be lower (P < 0.001) compared to other two groups. In polycystic ovary syndrome patients, ovulation induction with TMX resulted in inadequate response in more than half of the cycles. **Conclusions:** TMX can improve ET and live birth rate in patients with thin endometrium after clomiphene.

Keywords: *Clomiphene, gonadotropin, intrauterine insemination, tamoxifen, thin endometrium*

Introduction

Intrauterine insemination (IUI) is widely used as an empirical treatment for a large group of subfertile patients.[1] It is inexpensive, easy to perform, and more acceptable to the couple when compared to *in vitro* fertilization (IVF)/intracytoplasmic sperm injection.

Clomiphene citrate (CC) continues to be the most commonly prescribed drug for ovarian stimulation in IUI cycles. Despite ovulation rate of 50%–75%, pregnancy rate per cycle is observed in only 10%–20% of cases[2,3] due to peripheral anti-estrogenic effect at the level of the endometrium with clomiphene. Furthermore, endometrial thinning has been observed in 15%–50% of CC users.[4,5]

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To increase the endometrial thickness (ET), various strategies have been adopted to minimize the anti-estrogenic actions of CC but with limited success. Addition of systemic or vaginal estrogen along with CC treatment may increase ET.[6,7] Low-dose aspirin supplements[8] and intravaginal sildenafil[9] modify uterine vascularity and improve ET. Other methods such as starting CC earlier in the cycle,[10] use of aromatase inhibitors,[11] and delaying the administration of human chorionic gonadotropin (hCG)[12] have also been suggested. However, all these options to improve ET are controversial.

Treatment with gonadotropins and IUI has been shown to be highly successful in the treatment of patients having anti-estrogenic side effects with CC. Gonadotropin treatment raises several concerns, including the need for intensive monitoring, multiple pregnancy rate, which is equal to or higher than in IVF.[13]

Tamoxifen (TMX) closely resembles CC both in structure and mode of action. It appears to have agonistic action on the endometrium.[14] The increased estrogenic stimulation that has been observed with TMX action on the lower genital tract may be beneficial, especially for those suffering from an adverse response following the administration of CC. It was postulated that, by the administration of TMX, it might be possible to mimic the action of CC for the stimulation of ovarian follicles and avoid the adverse effects of CC on the endometrium.

The objective of the present study was to compare the efficacy of low-dose CC (50 mg), TMX, and gonadotropins in women with thin endometrium (<7 mm) following CC (100 mg) in IUI cycle.

Methods

This was a prospective observational study carried out at a private tertiary fertility center between December 2011 and June 2013. Approval was obtained from the Institutional Research Ethics Board (IRM/BNC-IHP 41/ October 20, 2010). Written informed consent was taken from all the women included in this study.

The whole cohort included 502 women between 25 and 38 years undergoing 932 IUI cycles for the following indications: Male factor, anovulation, and unexplained infertility [Figure 1]. All patients included had thin ET after 100 mg of CC in an earlier cycle. Pelvic ultrasonography was performed, and patients with any uterine or adnexal pathology were excluded from the study. Patients who had taken tuberculosis treatment in the past were excluded from the study. All male partners with a total motile sperm count of <5 × 10^6/ml were excluded from the study. Infertile polycystic ovary

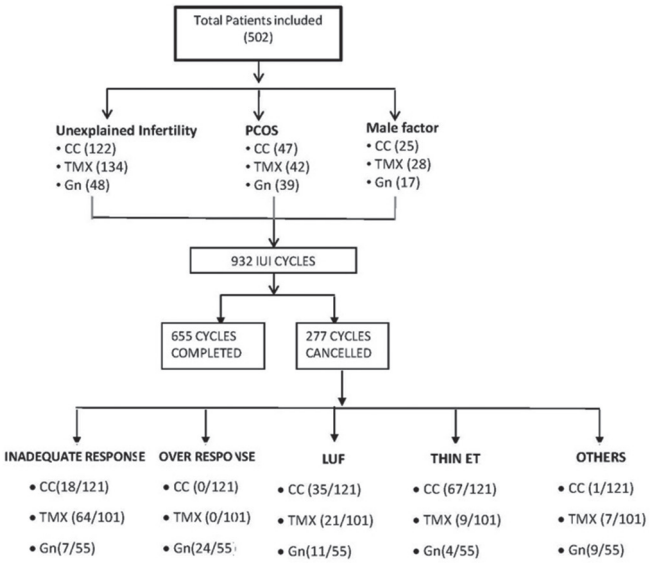

Figure 1: Number of patients, etiology, and performed intrauterine insemination cycle

syndrome (PCOS) women who had responded to CC previously, seeking IUI were included in the study.

A hysterosalpingogram was performed to verify tubal patency and patients with at least one tube patent were included in the study. Endometriosis patients were excluded from the study. PCOS was defined according to the modified Rotterdam revised ESHRE/ASRM criteria.[15] The diagnosis of unexplained infertility was based on normal findings in the seminal fluid analysis, mid-luteal serum progesterone, and hysterosalpingogram or laparoscopy.

A total of 502 women who had thin endometrium (<7 mm) after CC (100 mg) in IUI cycles were allocated into three groups in a serial order. Two months gap was given before ovulation induction in all three groups. Group A included 182 patients who had 364 stimulation cycles, received CC 50 mg/day from D3 to D7. Group B included 179 patients who had 342 stimulation cycles, received TM × 40 mg/day from D3 to D7. Group C included 141 patients who underwent 226 cycles, received urine-derived follicle-stimulating hormone (FSH) 75–150 IU starting from D3 till the day of hCG.

Transvaginal sonography for follicular monitoring was done from day 10 of menstruation onward. The internal diameter of each visible follicle was measured in two planes, and the average diameter was calculated. In addition, the ET was measured in the mid-sagittal plane from the outer to the outer edge of the endometrial-myometrial interfaces in the widest part of the endometrium. Ovulation was triggered with urinary hCG (5000 IU) when the leading follicle was ≥18 mm

and ET ≥7 mm. In patients with ET <7 mm, ovulation trigger was postponed till the ET was ≥7 mm. Women with persistent ET <7 mm and/follicle >24 mm were also excluded from the study. The cycle was cancelled in 24 patients who had ≥4 follicles with ≥16 mm diameter.

The primary outcome measure was live birth rate and secondary outcome variables were ET, number of mature follicles, ovulation rate, cancellation rate, pregnancy rate, and miscarriage rate.

Ethical clearance

This study was approved by our Institute's Ethical Committee (IRM/BNC-IHP-41/20-10-2010).

Statistical analysis

Multiple comparisons using one-way ANOVA and Schiff's test were performed, wherever appropriate, between the three Groups A, B, and C. Data are expressed as mean ± standard deviation; statistical significance of the test was performed at the 5% level ($P < 0.05$).

Results

A total of 277 cycles were cancelled out of 932 cycles. The major cause of IUI cancellations in TMX group was an inadequate response or failure to achieve even one follicle ≥16 mm. On the contrary, over the response that led to the presence of too many mature follicles (>4 follicles ≥16 mm) was the main cause of cancellation in the gonadotropin group (43.63%). In low-dose CC group, thin endometrium and luteinized unruptured follicle were the major cause of cancellation. On-demand failure to obtain a semen sample was the other reason for cancellation [Figure 1]. In PCOS, women response to TMX was inadequate in 55.2% of cycles which were cancelled [Table 1]. The clinical profile including age, duration of infertility, body mass index, baseline FSH, and luteinizing hormone of patients belonging to Group A, B, and C undergoing IUI is comparable [Table 2]. Different cycle parameters of the three groups are shown in Table 3. The ovulation rate was found to be comparable in all groups. ET was found to be significantly higher in both TMX and gonadotropin group compared to low-dose CC group. A number of follicles in the TMX group were significantly less ($P < 0.001$) compared to CC or gonadotropin group. However, size of the follicle was significantly higher in group A compared to other two groups on the day of hCG. When we compared the clinical outcome, TMX and gonadotropin group showed similar pregnancy rate (14.52% vs. 14.89%) and live birth rate (12.2% vs. 12.7%). However, in low-dose CC group both pregnancy rate ($P < 0.002$) and live birth rate ($P < 0.004$) were statistically lower compared to TMX or gonadotropin groups [Table 4]. There were three cases of twin pregnancy in gonadotropin group [Table 4].

Table 1: Inadequate response in polycystic ovary syndrome women

	Total PCOS cycles (241)	Cycles cancelled in PCOS (76)	Percentage
CC	91	16	16.4
TMX	96	53	55.2
Gn	54	7	12.9

CC=Clomiphene citrate, TMX=Tamoxifen, Gn=Gonadotropin, PCOS=Polycystic ovary syndrome

Table 2: Baseline characteristics

	CC (Group A)	TMX (Group B)	Gn (Group C)	*P*
Age	30±3.9	29.1±4.0	29.9±3.4	NS
BMI	21.9±2.1	22.3±2.2	22.8±3.4	NS
Duration of marriage	7.14±0.53	7.02±3.41	7.07±3.73	NS
FSH	6.2±1.5	5.9±1.6	5.9±1.4	NS
LH	5.15±1.4	4.79±1.2	4.68±1.11	NS

NS=Not significant, BMI=Body mass index, LH=Luteinizing hormone, FSH=Follicle-stimulating hormone, CC=Clomiphene citrate, TMX=Tamoxifen, Gn=Gonadotropin

Discussion

Our study has evaluated the role of TMX in ovulation induction compared to gonadotropin and low-dose CC in women with thin endometrium following 100 mg CC. ET is a well-established parameter for prediction of pregnancy in assisted reproduction technique. Studies have shown that pregnancy and implantation rates for the patients with ET >7 mm were significantly higher than those of patients who showed a thinner endometrium.[16,17] Furthermore, ET <8 mm on the day of hCG administration also increases the risk of biochemical pregnancy.[12] Thin endometrium, the most common anti-estrogenic effect of CC for ovulation induction has been seen in 15%–50% of patients.[5] This adverse effect of CC increases with higher doses.[18] Hence, in our study, we have included group A, in which the patients were stimulated with a lower dose of CC (50 mg) so that the antiestrogenic effect on endometrium may be reduced. Gonadotropins were used as the next line of management in this subset of women. Gonadotropin therapy, although more effective than CC, not only burdens the patient with stress and medical expense but can also cause multiple pregnancy and ovarian hyperstimulation syndrome. Therefore, preventing CC induced thinning of the endometrium by alternative methods like TMX/aromatase inhibitors appears imperative. During our study period, letrozole (aromatase inhibitor) was banned for use in ovulation induction.

TMX, primarily developed for use in the treatment of breast cancer, is a selective estrogen receptor modulator

Table 3: Cycle characteristics of the patients in different groups

	CC (Group A)	TMX (Group B)	Gn (Group C)	*P*
Ovulation rate (%)	66.75	71.63	78.6	NS
Cancellation rate (%)	33.24	29.53	24.34	NS
Number of follicles	2.2±0.58	1.3±0.49	2.3±0.49	AC (NS)
				AB (<0.001)
				BC (<0.001)
Size of follicles on the day of hCG	21.08±1.67	19.44±1.1	18.41±0.62	AB (<0.001)
				AC (<0.001)
				BC (<0.001)
ET	7.5±0.46	8.6±0.96	10.07±0.69	AB (<0.001)
				AC (<0.001)
				BC (<0.001)

AB=Group A versus Group B, BC=Group B versus Group C, AC=Group A versus Group C, ET=Endometrial thickness, NS=Not significant, hCG=Human chorionic gonadotropin, CC=Clomiphene citrate, TMX=Tamoxifen, Gn=Gonadotropin

Table 4: Pregnancy outcome

	CC (Group A), *n* (%)	TMX (Group B), *n* (%)	Gn (Group C), *n* (%)	*P*
Pregnancy rate	9 (4.94)	26 (14.52)	21 (14.89)	AB (<0.002)
				AC (NS)
				BC (NS)
Miscarriage rate	3 (1.64)	4 (2.2)	3 (2.1)	AB (NS)
				AC (NS)
				BC (NS)
Live birth rate	6 (3.2)	22 (12.2)	18 (12.7)	AB (<0.004)
				AC (<0.004)
				BC (NS)
Multiple pregnancy	1	Nil	3	AC (NS)

NS=Not significant, AB=Group A versus Group B, BC=Group B versus Group C, AC=Group A versus Group C, CC=Clomiphene citrate, TMX=Tamoxifen, Gn=Gonadotropin

that closely resembles CC in the mechanism of action. Published literature has reported ovulation rate of 50%–90% and pregnancy rate of 30%–50% following TMX.[19] Like CC, TMX occupies estradiol-binding sites on the hypothalamic-pituitary axis and prevents the negative feedback effect of estradiol, resulting in increased endogenous gonadotropin secretion.[20] Direct action on the ovary without involving hypothalamic-pituitary axis has also been suggested.[21] TMX unlike CC acts as an agonist on the endometrium and cervical mucus.[19] In the mid-luteal phase, TMX may enhance endometrial glycogen content thereby improving its receptivity.[21] Moreover, its use for ovulation induction for short duration is not associated with increased risk of ovarian and endometrial cancer.[22] Hence, it appears that TMX may be an alternative drug to gonadotropins in patients who had thin endometrium when treated with CC. Studies have observed that women having thin endometrium with CC (<7 mm) exhibited improved ET when TMX was used for ovulation induction in the subsequent cycle.[23,24]

A prospective study by Wang *et al*. compared TMX or CC along with alternate-day human menopausal gonadotropins for ovulation induction in patients with previously documented thin endometrium. They found that TMX group required longer duration and dose of gonadotropin stimulation with lesser number of mature follicles than CC group. They suggested that TMX may not be the first choice in patients with adequate endometrium, but they found a significantly increased ET and pregnancy rate in TMX group than CC.[24] In line with the above findings, our study also observed improved ET following TMX. The pregnancy rate and live birth rate in TMX group were comparable to gonadotropin group but significantly better than CC group. However, in PCOS women, we observed higher cycle cancellation rate following TMX due to inadequate response. This subset of women had shown a good follicular response to CC (100 mg) in the previous cycle. Therefore, it appears that TMX is not as efficacious as CC for ovulation induction in PCOS women. Similar to our observation, a randomized controlled trial conducted by Badawy *et al*. showed a significantly lower ovulation

rate following TMX compared to CC in PCOS women. They concluded CC had more ovulatory cycle than TMX in PCOS women.[25]

This is in contrast to the meta-analysis which concluded that there are no appreciable differences in ovulation or pregnancy rates after treatment with TMX or CC in anovulatory infertility.[26] Dhaliwal *et al*. reported TMX to be a good alternative to CC for ovulation induction in CC-resistant and CC failure PCOS patients. They had started with TMX 40 mg/day and increased it to 80 mg/day in nonresponders.[27] A recent Cochrane review comparing the efficacy of anti-estrogens in PCOS women also reported similar pregnancy and live birth rates with CC and TMX.[28]

In our study, we have noted that the size of leading follicle in CC group on the day of hCG trigger was greater ($P < 0.001$) compared to the gonadotropin and TMX group. This is because many patients in the CC group had ET <7 mm when the follicular size reached ≥18 mm, and hence, hCG administration was delayed till ET reached ≥7 mm, which resulted in greater follicular diameter. We also observed higher luteinized unruptured follicles in CC group. The number of cancellations due to over response following gonadotropins was higher probably due to increase in dose of gonadotropin on day 7, when inadequate response was noted. Although the mechanism of action is similar in both TMX and CC, we observed a significantly lesser number of follicles following induction with TMX.

Conclusions

TMX (40 mg) appears to be a promising drug in women with thin endometrium following CC (100 mg). It seems to be less effective in women with PCOS who responded well with CC (100 mg). Further larger well-designed trials are warranted to support the findings.

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Conflicts of interest

There are no conflicts of interest.

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