Original Article

Tamoxifen for ovulation induction in infertile PCOS women who did not conceive with 3 or more cycles of clomiphene citrate: A prospective clinical study

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Abstract

Objectives: To assess the ovulatory, pregnancy rates and side effects of tamoxifen (TMX) in women who are infertile with polycystic ovarian syndrome (PCOS) and who did not conceive with three cycles of clomiphene citrate (CC).

Study Design: A prospective interventional study.

Population: Seventy-four women who were infertile with PCOS and who did not achieve pregnancy after a minimum of three cycles of CC were included in the study.

Materials and Methods: TMX was given orally from Day 2 to Day 6 of the menstrual cycle, with a dose of 40 mg in the 1st cycle and 80 mg in the subsequent two cycles. Transvaginal ultrasound was used for follicular monitoring from Day 10 and on every alternate day till the day of ovulation or till the 20th day of the cycle.

Statistical Analysis: Ovulation rates with different doses were compared using McNemar test. Kruskal–Wallis test was used to find out differences in maximum follicular diameter and endometrial thickness (ET) between 3 cycles.

Results: The mean maximum follicular diameter was 16 ± 5.2 mm, and the mean ET was 8.9 ± 1.7 mm with an ovulatory rate of 41.90% with 40 mg of TMX. Mean increase in the maximum follicular diameters with 80 mg of TMX was higher when compared with 40 mg (*P* value − 0.000) of TMX. Increasing the dose of TMX in cycles 2 and 3 resulted in a statistically significant increase in the ovulatory rates; however, it was not so with ET. There were no clinical pregnancies, and minor side effects occurred in 14.1% of the participants.

Conclusion: TMX induced ovulation only in 56% of the participants, and optimum ET was achieved in 92.7% of the participants; in addition, there were no pregnancies. Hence, TMX is not a useful ovulation inducing agent for CC failure/CC-resistant PCOS.

Keywords: CC failure, infertility, ovulation induction, PCOS, tamoxifen

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INTRODUCTION

Worldwide, polycystic ovarian syndrome (PCOS) is the most common cause of anovulatory infertility accounting for 20–25% of all cases of infertility.[1] The introduction of clomiphene citrate (CC) for ovulation induction in 1962 has revolutionized the management of PCOS infertility, but the high rates of ovulation achieved with

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CC[2,3] could not be converted to equally high rates of pregnancy.[4,5] This discrepancy could be attributed to the antiestrogenic effects of CC on the cervical mucus and the endometrium.

Tamoxifen (TMX), which is traditionally used in the management of breast carcinoma, is currently being examined for its potential to achieve successful ovulation and conception in women who have CC-resistant PCOS because of its favorable effects on the cervical mucus and endometrium.[6]

There are studies that have documented the relative effects of clomiphene and TMX on the pregnancy rates in women with PCOS;[7] however, most of them were inconclusive. Some studies showed no appreciable differences in ovulation or pregnancy rates after treatment with either of these drugs,[8] whereas others have found either lower[9] or better ovulatory and pregnancy rates with TMX.[10] Hence, this study aimed to determine the ovulatory and pregnancy rates with TMX in women who were infertile with PCOS and who failed to conceive with clomiphene; in addition, the side effects of TMX in doses used for ovulation induction were studied.

MATERIAL AND METHODS

This was a prospective interventional study conducted in accordance with the ethical standards of the ethics committee on human experimentation of our institute (ECR/342/Inst/PY/2013). Approval for the use of TMX for ovulation induction was obtained from the Drugs Controller General of India (CT/Drugs/12/2015). Eighty-one women who were infertile with PCOS, diagnosed as per Rotterdam criteria[11] and aged between 21 and 40 years, and who did not conceive with a minimum of three cycles of CC were included in the study after obtaining a written informed consent. To detect up to 25% pregnancy rates with patients treated with TMX in accordance with a study conducted by Dhaliwal *et al.*,[12] sample size was estimated to be 73. Calculations were performed with Openepi software, with 10% absolute precision. Assuming a 10% dropout/loss to follow-up rates, final sample size was estimated to be 81.

A comprehensive work-up of infertile patients including detailed history, clinical examination and relevant investigations of both partners was carried out. TMX at a dose of 40 mg was given orally from Day 2 to Day 6 of the menstrual cycle in the 1st cycle. Follicular monitoring was performed by transvaginal ultrasound using a Voluson E-8 (GE Healthcare Austria GmbH & Co OG, Austria) machine at 7.5-MHz probe frequency starting from Day 10 and on every alternate day till the day of ovulation or till the 20th day of the cycle. The dimensions of the dominant follicle were measured in anteroposterior and transverse planes and expressed in millimeters.

The occurrence of ovulation was determined by one or more of the following criteria:

- The development of a dominant follicle of size ≥17 mm followed by its disappearance;
- A change in the shape of the follicle or the appearance of internal echoes within the follicle; and
- Free fluid in the pouch of Douglas.

Endometrial thickness (ET) was measured considering the thickest echogenic area and was measured from one basal endometrial interface, across the endometrial canal, to the other basal endomyometrial interface.

The participants were advised to have timed coitus, and no other interventions such as intrauterine insemination were performed. The occurrence of pregnancy was confirmed clinically and by the ultrasound visualization of the gestational sac.

If ovulation did not occur or if ovulation occurred but did not result in pregnancy, then the dose of TMX was increased to 80 mg/day for cycles 2 and 3, and the patients were monitored for ovulation and conception as aforementioned. Any side effects with TMX therapy such as hot flushes, vaginal bleeding, vaginal discharge, pruritus vulvae, or general side effects such as gastrointestinal intolerance, headache, lightheadedness and, occasionally, fluid retention, and alopecia were noted. Any rare side effects such as bone pain, venous thromboembolism, retinopathy, and ovarian cysts were also looked for. The parameters included for statistical analysis were maximum follicular diameter prior to ovulation, ET preceding ovulation or at ovulation, ovulation, pregnancy, and side effects of TMX.

STATISTICAL ANALYSIS

Data was entered in MS Excel spreadsheet, and analysis was performed using the Statistical Package for the Social Sciences version 20.0 software (IBM SPSS Software, United States). Quantitative variables such as age and body mass index (BMI), were categorized as per standard criteria and were expressed as mean and standard deviation. Categorical variables such as the type of

infertility, BMI categories, the number of years of infertility, prior treatment cycles, and associated medical illnesses, were summarized in terms of percentages. Mann–Whitney test was used to compare the parameters across parameters such as thyroid status. Chi-square test was used to assess the association between the categorical variables. Side effects noted during the study were expressed as percentages.

Discrete variables such as maximum follicular diameters and ET were expressed as mean and standard deviation. For a comparison of the non-normally distributed variables across time, that is, between three cycles, Friedman test was used. If Friedman test was significant, comparison was made between two levels using Wilcoxon signed rank test. Ovulation rates were expressed as percentages. Ovulation rates with different doses were compared using McNemar test. Statistical significance was considered at <0.05 level.

To compare the differences of maximum follicular diameter and ET between groups based on glucose tolerance test, Kruskal–Wallis test was used.

RESULTS

Out of the 81 participants enrolled in the study, 74 women were included in the analysis. Seven participants were lost to follow-up. The clinical profiles of the women are summarized in Table 1. The mean age of the study participants was 26.5 years, and three-quarters of them presented with primary infertility. Though the mean BMI was 24.5, majority (46%) of the participants were obese. The mean duration of infertility was 5.1 years, and these women had been treated with on an average five cycles of CC prior to enrolment in this study. Forty-five percent of these women had associated medical or endocrine abnormalities contributing to their infertility. Twenty women had hypothyroidism (27%), and five women were diagnosed with hyperprolactinemia during baseline investigations performed for the study. About 90% of the women reported to be having menstrual irregularities in the form of oligomenorrhea since menarche. More than half of the study participants were noted to have hirsutism with modified Ferriman–Gallwey score ≥ 8. Acne was, however, observed in only 10.8% of the women studied.

Maximum follicular diameters were measured in millimeters during every ultrasound visit in all the three cycles, and the maximum follicular diameters achieved prior to ovulation with the different doses of TMX are represented in Table 2. Mean follicular size achieved with a TMX dosage of 40 mg from Day 2 to Day 6 was 16 ± 5.2 mm during the 1st cycle. With 80 mg dosage of TMX, the mean follicular diameter was 17 ± 4.9 mm in the 2nd cycle. About 30% of the participants had a follicular dimension of more than 20 mm, and 49 of the 74 women developed follicles of more than 16 mm in maximum diameter during the 3rd cycle with 80 mg dose of TMX. The optimum ET of 7–10 mm was achieved in more than 75% of the women in all cycles.

The maximum follicular diameter during the three cycles is represented in Table 3. The follicular diameter increases with increasing doses of TMX, which is statistically significant.

The ET achieved prior to ovulation is represented in Table 4. There was no significant increase in the mean ET value with increasing doses of TMX.

Table 1: Clinical profile

S. no.	Clinical profile	Total number ($n = 74$)	Percentage (%)	Mean ± SD
1	Age			
	21–25 years	34	45.9%	26.5 ± 3.3 years
	26–30 years	32	43.2%	
	31–35 years	7	9.5%	
	36–40 years	1	1.4%	
2	BMI			
	Lean PCOS	5	6.8%	24.5 ± 5.42
	Normal BMI	25	33.80%	
	Overweight	10	13.50%	
	Obese PCOS	34	45.90%	
3	Hyperandrogenism			
	Hirsutism	43	58.1%	
	Acne	8	10.8%	
4	Type of infertility			
	Primary infertility	58	78.4%	–
	Secondary infertility	16	21.6%	
5	No. of years of infertility			
	1–6 years	52	70.2%	5.1 ± 2.9 years
	7–12 years	19	25.7%	
	≥12 years	3	4.1%	
6	No. of cycles of clomiphene citrate received			
	3 cycles	23	31.08%	5.02 ± 2.17 cycles
	3–6 cycles	37	50%	
	>6 cycles	14	18.91%	
7	History of laparoscopic ovarian drilling	6	8.1%	–
8	Medical/endocrine disorders	34	45.9	
	Impaired glucose tolerance	2	2.7%	–
	Type II DM	5	6.8%	
	Hypothyroidism	20	27%	
	Hyperprolactinemia	5	6.8%	
	Other disorders	5	6.8%	

Table 2: USG monitoring of follicular growth and endometrial thickness

S. no.	Parameter	1st cycle		2nd cycle		3rd cycle	
		n = 74	(%)	*n* = 74	(%)	*n* = 74	(%)
1	Maximum follicular diameter						
	≤10 mm	5	6.76%	4	5.41%	3	4.05%
	10–16 mm	40	54.05%	28	37.84%	22	27.73%
	>16–18 mm	7	9.46%	17	22.97%	16	22%
	>18–20 mm	4	5.41%	4	5.41%	12	16.22%
	≥20 mm	18	24.32%	21	28.38%	21	28.38%
2	Endometrial thickness						
	<7 mm	3	4.05%	2	2.70%	–	–
	7–10 mm	57	77.03%	59	79.73%	59	79.73%
	>10–12 mm	11	14.86%	9	12.16%	11	14.86%
	>12 mm	3	4.05%	4	5.41%	4	5.41%

Table 3: Tamoxifen and maximum follicular diameter prior to ovulation

Cycle	Dose of tamoxifen	Maximum follicular diameter (mm)	95% CI	*P*-value
		Mean ± SD		
1st cycle	40 mg	16 ± 5.2	14.8–17.2	0.000
2nd cycle	80 mg	17 ± 4.9	15.9–18.1	
3rd cycle	80 mg	18 ± 4.1	17.1–18.9	

The ovulatory rates with increasing doses of TMX are represented in Tables 5 and 6. There was a statistically significant increase in ovulatory rates [95% confidence interval (CI)] with increasing doses.

Pregnancy rates

All the 74 patients were followed up for identifying clinical or biochemical evidence of pregnancy, but no successful pregnancies could be documented in them. The patients were followed up for 3 months after the 3rd cycle, and two patients became pregnant in their natural cycles within 3 months.

Side-effects

Only 14.9% of the women had minimal side effects during the study, and these are shown in Table 7. Among these, three women reported alteration in the bleeding pattern in subsequent cycles with 80 mg of TMX, and four women had mild gastrointestinal disturbances such as nausea and bloating sensation in all the three cycles. Four women developed clear ovarian cysts during the course of the study; two women developed similar changes with 40-mg dose, and the other two developed these changes with 80-mg. These cycles were suspended, and the women were followed up. None of the study participants had severe side effects such as alopecia, visual disturbances, or deep vein thrombosis.

When women with endocrine abnormalities were analyzed, the ovulatory rates were low, and ovulation was achieved only with 80-mg TMX in more than 50% of the participants. This was especially true for women with hypothyroidism [Table 8].

Table 4: Comparison of endometrial thickness with increasing doses of tamoxifen

Cycle	Dose of tamoxifen	Endometrial thickness (mm) Mean ± SD	95% CI	*P*-value
1st cycle	40 mg	8.9 ± 1.8	8.5–9.3	0.097
2nd cycle	80 mg	9.1 ± 1.6	8.7–9.5	
3rd cycle	80 mg	9.2 ± 1.6	8.8–9.5	

Table 5: Endometrial thickness with increasing doses of tamoxifen

Cycle	Dose of tamoxifen	No. of participants ovulated (*n*)	Percentage (%)	95% CI
1st cycle (*n* = 74)	40 mg	31	41.9%	31.3–53.2
2nd cycle (*n* = 74)	80 mg	44	59.5%	48.1–69.9
3rd cycle (*n* = 74)	80 mg	54	73.0%	61.9–81.8

Table 6: Level of significance in ovulatory rates

1st and 2nd cycles	*P* = 0.004
1st and 3rd cycles	*P* = 0.000
2nd and 3rd cycles	*P* = 0.002

Table 7: Side effects

Side effect	Number (*n* = 11)	Percentage (%)
Altered bleeding pattern	3	4.1%
Gastrointestinal symptoms (nausea, bloating)	4	5.4%
Ovarian cysts	4	5.4%
Alopecia	–	–
Blurred vision	–	–
Deep vein thrombosis	–	–

DISCUSSION

Extensive research has been undertaken to overcome CC resistance, and TMX is one of such drugs explored in few studies, including this study. Majority of the participants in

Table 8: Endocrine abnormalities and response to tamoxifen

S. no.	Endocrinopathy ($n = 29$)	Mean follicular diameter (mm)			Endometrial thickness (mm)			Ovulatory rates (%)		
		1st cycle	2nd cycle	3rd cycle	1st cycle	2nd cycle	3rd cycle	1st cycle	2nd cycle	3rd cycle
1	Impaired glucose tolerance ($n = 2$)	21.5	23.5	21.5	8.4	7.7	7.7	50%	100%	100%
2	Type II DM ($n = 2$)	12	13	13	9.25	8.4	8.3	0%	0%	50%
3	Hypothyroidism ($n = 20$)	17	18	20	9	9	9.2	30%	65%	80%
4	Hyperprolactinemia ($n = 5$)	18	18.5	17	8.1	8.6	8.6	60%	60%	80%

this study belonged to the age group of 21–25 years, with a mean age of 26.5 ± 3.3 years. This observation is comparable to the study,[15] which employed TMX in CC resistant PCOS with a mean age of 26.2 ± 1.1. The younger age range of the participants in this study's cohort may be explained by the practice of early marriage that is rampant in the society where the study was conducted. Obesity exacerbates the metabolic and reproductive abnormalities in women with PCOS. Studies have shown that about 40–80% of women with PCOS are either overweight or obese signifying interrelated genes or environmental factors.[13] This study with a mean BMI of 24.5 ± 5.42 confirms these findings. In a study describing the prevalence of PCOS and the features of women with PCOS,[14] about 8.2% of women with PCOS were noted to be underweight, which was similar to this study, in which 6.8% of the women were lean PCOS.

The distribution of cases into primary and secondary infertility in this study (78.4% versus 21.6%) was similar to a study by Dhaliwal *et al.* (80% versus 20%).[12] Majority (70.2%) of this study's population had about 6 years of infertility, which was slightly lesser in comparison with the aforementioned study, which had 84.3% women with up to 6 years of infertility.

About three-fourths of this study's population (75.7%) received up to six cycles of clomiphene before being enrolled in the study, and about 10% of the women had received up to eight cycles. CC failure or resistance has varied definitions throughout the literature. A study by Gulekli *et al.*[11] administered TMX to 20 patients who failed to ovulate with CC at a dose of 200 mg/daily at least in three subsequent cycles and considered them to be CC resistant. In a study by Dabbaghi and Mardani,[16] thirty-four women were treated with 150 mg CC for 5 days; if they failed to develop a dominant follicle or a ET ≥7 mm, they were considered to be clomiphene resistant and were administered TMX.

As a tertiary care center, women arrived from different regions, where they would have received varied doses of CC for varying number of cycles; in addition, sometimes the occurrence of ovulation was not documented correctly. Hence, we included women who failed to conceive with at least three cycles of CC, irrespective of the dose, as our study population.

Some studies that compared clomiphene with TMX for ovulation induction in women with PCOS have used different doses of TMX ranging from 10 to 80 mg. Studies[16-18] that specifically addressed the role of TMX in women with CC-resistant PCOS have compared the usage of 10 mg of TMX with 20 mg and 20 mg of TMX with 40 mg, respectively; these studies reported better ovulation and pregnancy rates with higher doses of TMX. In this study, the dosage of 40 mg in the 1st cycle followed by 80 mg in the subsequent cycles is based on a recent Indian prospective study[12] that had employed similar doses and achieved significant ovulation and pregnancy rates in women with CC-resistant PCOS.

In this study, the mean follicular diameter achieved with 40 mg of TMX was 16 ± 5.2 mm, and about 50% of the women developed a follicle of size ≥16 mm, which was greater than an Iranian study[16] that administered TMX to 34 women who were CC resistant and infertile and reported that with a 30-mg dose of TMX, nine patients (23.4%) developed a dominant follicle.

In this study, 63.5 and 74.3% of the women developed a dominant follicle in the 2nd and 3rd cycles respectively with 80 mg TMX. These results are similar to a prospective comparative study[17] in 2007, which compared the development of dominant follicles with 40 mg and 60 mg of TMX and stated that 63% of those in the study's cohort developed a dominant follicle with 60-mg TMX.

In this study, an attempt was made to exploit the dual benefits of TMX, both as an ovulation-inducing agent and for its estrogenic stimulation effects on the endometrium of these patients. It is believed that increase in ET with TMX therapy is due to the direct action of TMX on the endometrium and not as a consequence of higher serum estradiol concentration from more stimulated follicles. Though the exact

thickness of the endometrium, which is incompatible for establishing a successful pregnancy, is unknown and depends on the type of ovulation induction protocol employed, a thicker endometrium is generally associated with better pregnancy rates.

A prospective case–control study that compared multiple treatment protocols found no live births when the ET was <6 mm.[18] The study group in this study consisted of women who failed to conceive with CC due to various reasons, one of which might be due to a thinner mid-cycle endometrium present in women taking CC than in women with a natural cycle.[19] Mean ET in this study with 40-mg TMX was 8.9 ± 1.79 mm, with an increase to 9.1 ± 1.5 mm with 80-mg TMX in the 2nd and 3rd cycles. Though this improvement in ET between 40 and 80 mg is not statistically significant, it may be clinically significant in women with CC resistance.

Mean ET in this study is comparable to an Indian study that evaluated the role of ET in predicting successful pregnancies and found that 55.5% of the pregnancies occurred when the mean ET was between 8 and 10 mm.[20]

With 40-mg dose, the mean ET of 8.9 mm in this study was similar to the mean ET achieved with the same dose in studies by Dhaliwal *et al.*[12] and Reynolds *et al.*[21] but was less compared to the mean ET of 10.8 ± 2.3 mm achieved in a study by Wang *et al.*,[22] who administered TMX with alternate-day gonadotropin in patients with thin endometrium. In a study by Pant,[17] with 80-mg dose, majority of the women had an ET of 8–13 mm, which was in agreement with this study, wherein 82.3% of the women had an ET of 8–13 mm.

Successful ovulation in 124 of the total 222 cycles, accounting to 55.8% ovulatory cycles, as found in this study is consistent with other similar studies, which reported an ovulation rate of about 40–67% with TMX in women who were nonresponsive to clomiphene.[20,21] Thirty-one of the 74 women administered with 40 mg of TMX ovulated, and 98 of the 148 cycles with 80-mg TMX were ovulatory, accounting to a statistically significant increase in ovulation rate from 41.9% in the 1st cycle to 66.2% in the 2nd and 3rd cycles.

Several studies have compared the ovulation rates with varying doses of TMX and found better rates of ovulation and pregnancy with a higher dose of TMX. One such study was from India,[12] and was similar to this study in that it also compared the ovulation rates between 40 and 80 mg of TMX. They reported an ovulation rate of 65.2% with 40 mg of TMX, which was higher than the ovulation rate achieved in this study, and 75.8% with 80 mg of TMX, which was comparable. However, the aforementioned study included all women with PCOS and not just women with CC-resistant PCOS. This study had a subgroup analysis among women who were CC resistant and reported an ovulation rate of 31.4 and 14.6% with 80 mg and 40 mg of TMX, respectively. In 2004, Nardo[10] also compared ovulation rates with 20 mg versus 40 mg TMX and reported ovulation rates of 67.2 and 54%, respectively. Studies that dealt with the use of TMX in women who were CC resistant are summarized in Table 9.

Studies[12,15,16] using TMX for ovulation induction have reported pregnancy rates ranging from 15 to 30% with varying doses of TMX. Though this study achieved the rates of ovulation similar to these studies, the study population could not conceive with TMX within three cycles. The possible explanation why many of these women also failed to conceive with multiple cycles of CC administered prior to participation in this study could be because there might be other inherent patient factors coexisting, leading to infertility, which need further exploration.

Though TMX resulted in a favorable endometrium in terms of thickness in many of these women, its effect on the endometrial echotexture and endometrial receptivity, which requires the expression of genes that facilitate implantation, has not been studied in this study. Recent advances in the study of molecular

Table 9: Tamoxifen in CC resistant PCOS

S. no.	Year of the study	Author	No. of participants	Dose of tamoxifen	Ovulation rate	Pregnancy rate
1	1987	Weseley and Melnick[17]	17	10 mg	11.7%	–
2	1993	Gulekli *et al.*[15]	10	20 mg	10%	–
			10	40 mg	70%	30%
3	2007	Dabbaghi and Mardani[16]	34	30 mg	23.4%	5.8%
4	2011	Dhaliwal *et al.*[12]	70	40 mg	–	14.6%
				80 mg		31.4%
5	2016	Current study	74	40 mg	41.90%	–
				80 mg	59.50%	–
				80 mg	73%	–

aberrations in implantation failure and recurrent pregnancy losses have highlighted the importance of certain cytokines and interleukins (IL) such as IL-1, IL-11, LIF, IL-12 and IL-18, integrin αvβ3, glycodelin, and polymorphic mucin 1 in synchronizing the dialogue between the endometrium and the embryonic tissues. The effect of TMX on implantation, which is the initial step toward the establishment of a successful pregnancy, has not been analyzed in this study. This might have been a cause for the failure of conversion of high ovulatory rates to high pregnancy rates in this study.

Endocrinopathies such as hypothyroidism, diabetes, and hyperprolactinemia were noted in about 40% of this study's population. Hypothyroidism was noted in 27% of the women enrolled, which was slightly higher than a study that stated that 23% of the women in southern India especially the Tamilnadu–Pondicherry belt had overt hypothyroidism. One in every three women enrolled in this study was found to be hypothyroid, the values of which were much higher than the Indian study which stated that one in every eight young south Indian women was hypothyroid.[23] Biochemical hyperandrogenemia was noted in 23% of the women, whereas, approximately, 70% of the study's population had clinical evidence of hyperandrogenism in the form of hirsutism. This was comparable to studies that reported that about 60–80% of the women with PCOS had features of hyperandrogenism.

Though optimally corrected, endocrine abnormalities might have negatively modulated the hypothalamic–pituitary hormones responsible for gonadal function, which might have resulted in the lack of clinical pregnancies in this study. Although two patients conceived within the follow-up period of 3 months after the 3rd cycle, it is difficult to explain such an observation. This finding could be attributed to chance, or, perhaps, there might be some degree of clinical "carry over" after the administration of TMX, and women may conceive in the cycles immediately after induction. However, the relative significance of this observation remains uncertain; it is hoped that future studies prove or disapprove these findings.

Between 10 and 23% of the cases of female infertility are attributed to endocrine dysfunction. In this study, an attempt was made to analyze the differences in the effect of TMX in women with endocrine abnormalities in comparison with women without associated endocrine abnormalities. The prevalence of hypothyroidism (27%) and hyperprolactinemia (6.8%) in this study's population was similar to other studies[24] that reported a high prevalence of these endocrine disorders in women with anovulatory infertility. Though this study was not powered enough to find a statistical significance, we found that women with endocrine abnormalities in general ovulated at a higher dose of TMX. This could be due to the inherently abnormal hormonal milieu in these patients precluding a successful ovulation or abnormal endometrial molecular development. Though not statistically significant, this information is clinically relevant because it stresses the importance of adequately treating these endocrine disorders before embarking on the induction of ovulation in these women.

No dangerous side effects of TMX such as deep vein thrombosis or visual disturbances were noted in this study. Few women complained of an altered pattern of bleeding in their subsequent cycles, and few others complained of gastrointestinal disturbance. Four women (two women with 40-mg dose and two women with 80-mg dose) developed clear ovarian cysts in this study. On further analysis, these women were noted to be aged more than 30 years, had primary infertility, received five to six cycles of CC prior to TMX, and had no associated medical illness or endocrine abnormality. The development of ovarian cysts with TMX in premenopausal women with endogenous estrogens is documented in several other studies. A prospective nonrandomized trial[25] found a high incidence of ovarian cysts in premenopausal women on TMX, but the authors reinforced the fact that these cysts were transitory in nature and required only expectant management and follow-up with ultrasound.

CONCLUSION

TMX induced ovulation only in 56% of women with CC failure/CC-resistant PCOS. Ovulatory rate significantly increased with the increasing doses of TMX up to 80 mg. Optimum ET (7–12 mm) was achieved in 92.7% of the women. There were no clinical pregnancies during the study period and minor side effects occurred in 14%. Hence, TMX is not a useful ovulation inducing agent for women with CC failure/CC-resistant PCOS and cannot be recommended for the management of infertility in a similar cohort.

Limitations

LH kits were not used for diagnosing ovulation. Serum estradiol was not used for follicular growth monitoring.

Endometrial architecture and Doppler flow were not studied.

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Conflicts of interest

There are no conflicts of interest.

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