

Comparison of tamoxifen and clomiphene citrate for induction of ovulation in cases with thin endometrium

Original
Article

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ABSTRACT

Introduction: One of the earlier and most common drugs that have been used for ovulation induction is clomiphene citrate (CC), recently, other agents have been introduced to avoid the side effects of clomiphene citrate. Tamoxifen is another anti estrogenic compound that may be effective for ovulation induction in cases with thin endometrium. The aim of the study was to compare the efficacy of tamoxifen versus low dose clomiphene citrate for ovulation induction in cases with thin endometrium.

Patients and Methods: After the ethics committee approval, this randomized clinical study was conducted among 82 infertile women with thin endometrium (<7mm) and presented to the Gynecology outpatient clinic. The participants were divided randomly into two equal groups, seventy-eight women completed the study. Group A included 40 patients receiving tamoxifen while group B included 38 patients receiving clomiphene citrate (CC).

Results: Mean number of mature follicles ≥ 18 mm was 1.7 ± 0.6 in group A and 1.9 ± 0.8 in group B ; the difference was statistically insignificant (p -value = 0.2). Endometrial thickness (ET) was significantly different between both groups; it was higher in tamoxifen group than clomiphene citrate group (8.9 ± 1.2 mm versus 7.2 ± 1.1 mm, $p < 0.0001$). Also, it was noted that there were significant statistical discrepancies between both groups regarding pregnancy rate and ongoing pregnancy rate, as they were 22.5% and 17.5 % in group A and 5.3% and 2.6%, respectively, in group B ($p < 0.05$).

Conclusion: Tamoxifen has valuable effect on endometrial thickness, tamoxifen increases endometrial thickness and livebirth rate in patients with thin endometrium.

Key Words: Clomiphene citrate, ovulation induction, tamoxifen, thin endometrium.

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INTRODUCTION

One of the earlier drugs that have been introduced for ovulation induction is clomiphene citrate (CC). It has been introduced in the early 1960s and for more than 50 years, it has been used widely as the most common oral agent for ovulation induction^[1, 2]. With marked discrepancy between low pregnancy rate (30-40%) which is not as high as the ovulation rate (70-80%)^[3]; there had been a strong urge to search for new oral agents for ovulation induction.

In the recent past, tamoxifen, a triphenylethylene derivative, is another anti estrogenic compound with structure very similar to CC^[4]. It has been evaluated for ovulation induction and reported ovulation rates were 50-90% and pregnancy rates were 30-50% with good results in CC failure cases and absence of CC side effects as ovarian hyper stimulation and multiple pregnancies^[5].

Of great concern, tamoxifen improves folliculogenesis process by blocking oestradiol-binding

sites on the hypothalamic-pituitary axis and preventing the negative feedback effect of oestradiol, so increasing gonadotrophin secretion^[6], better functioning of the corpus luteum^[7], in addition to beneficial effects on the cervical mucus^[8] and increased endometrium receptivity power^[7]. Therefore, tamoxifen may be used as either an alternative or synergetic agent to increase pregnancy rates^[9].

Endometrial thickness (ET) is important for successful pregnancy after ovulation induction. Different agents have been used to minimize the anti estrogenic actions of CC such as estrogen^[10] low dose aspirin^[11] and sildenafil^[12]. So, the present study aimed to compare the efficacy of tamoxifen versus low dose clomiphene citrate for ovulation induction in cases with thin endometrium.

PATIENTS AND METHODS

After approval of the ethics committee of Faculty of Medicine, Suez-Canal University, this randomized clinical trial was conducted among 82

infertile women with thin endometrium (<7mm) during the period from January 2014 to March 2017. The study included women in reproductive age 20-35 years, BMI < 30 kg/m², normal hormonal profile [follicle-stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH) and prolactin hormone], normal uterine cavity and patent fallopian tubes based on previously performed documented hysterosalpingography (HSG) or laparoscopy. Male factor was excluded by semen analysis. An explanation of the study and a signed consent sheet was obtained from all participants. Women attended or referred to the outpatient clinics were randomized into two equal groups, seventy-eight women completed the study. Group A included 40 patients receiving tamoxifen, while group B included 38 patients receiving clomiphene citrate. Infertile women with thin endometrium (<7mm) was diagnosed in the previous cycle after induction of ovulation with 100 mg of CC for 5 days. Women who had an adequate follicular response on CC and unsatisfactory endometrial thickness (<7 mm) were shifted randomly in the subsequent cycle to 40 mg tamoxifen (Tamofen®, Al-Amarya CO., Egypt) daily starting from the 3rd day to the 7th day of the cycle (group A) or 50 mg clomiphene citrate (Clomid®, Global Co., Egypt) (in group B). In both groups, all women underwent ultrasonography on the 3rd day of the menstrual cycle to exclude ovarian cysts, serial folliculometry was done by transvaginal sonography (TVS) every other day starting from the 9th day of menstrual cycle (ultrasound was done by only one observer). Endometrial thickness was assessed prior to HCG administration, it was measured by transvaginal sonography in a sagittal plane in the fundus of the uterus on day 12. Human Chorionic Gonadotrophin (HCG) at a dose of 10000 IU was administered intramuscularly (Epifassi®, EPICO CO., Egypt) when at least one follicle with a mean diameter ≥ 18 mm or at least two follicles ≥ 16 mm were observed [13]. Timed intercourse was advised 24 to 36 hours after Human Chorionic Gonadotropin (HCG) injection. After 24 hours of the timed intercourse, all patients received 200 mg of progesterone vaginally (Prontogest®, Marcyrl CO., Egypt) daily for 2 wks. The primary outcome measures included endometrial thickness and number of mature follicles, while secondary outcome measure was pregnancy rate after one cycle of treatment protocol.

Pregnancy was checked by serum beta human chorionic gonadotropin. Clinical pregnancy was defined as the detection gestational sac by transvaginal ultrasound examination at the 6th week gestation. Ongoing pregnancy was recorded when pregnancy passed to 13 weeks of gestational age.

Statistical analysis

Data were processed using SPSS version 15 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as means ±SD and qualitative data were expressed as numbers and percentages. Student's T-test was used to test significance of difference for quantitative variables while Chi-square test was used to test significance for qualitative variables. A probability value (*p-value*) < 0.05 was considered statistically significant.

RESULTS

Eighty-two infertile women with thin endometrium were randomized into two equal groups, seventy-eight women completed the study. Group A included 40 patients receiving tamoxifen while group B included 38 patients receiving clomiphene citrate (fig. 1).

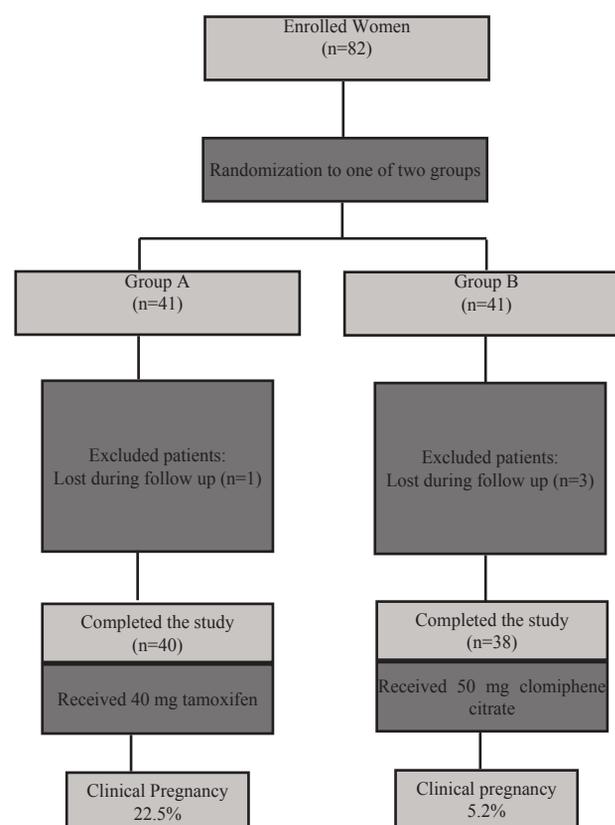


Fig. 1: Flow chart of the studied population

Table (1) shows that patients of both groups were matched regarding age, Body Mass Index (BMI), duration and type of infertility. Mean age was 28.6 ± 5.2 years and 27.3 ± 4.4 years in group A and group B, respectively, (*p-value*=0.23). Mean BMI was 25.8 ± 2.9 and 26.4 ± 3.2 in group A and group B,

respectively; there was no statistically significant difference (p -value= 0.39). Our results showed that 80 % of patients in group A and 86.8 % of patients in group B had primary infertility (p -value= 0.42). Mean duration of infertility was 4.6 ± 2.1 and 4.2 ± 1.9 years in group A and group B, respectively; the difference was statistically insignificant ($p > 0.05$).

Table 1. Baseline characteristics between studied patients in both groups

Characteristics		Tamoxifen group (n=40)	Clomiphene group (n=38)	p-value
Age (Years)	Mean \pm SD	28.6 \pm 5.2	27.3 \pm 4.4	0.23 (NS)
BMI (kg/m ²)	Mean \pm SD	25.8 \pm 2.9	26.4 \pm 3.2	0.39 (NS)
Type of infertility	Primary	32 80%	33 86.8%	0.42 (NS)
	Secondary	8 20%	5 13.2%	
Duration of Infertility	Mean \pm SD	4.6 \pm 2.1	4.2 \pm 1.9	0.38 (NS)

NS: No statistically significant difference, BMI: body mass index

The main outcome measures of this study were presented in Table (2). Interestingly, group A was superior than group B as regarding most of the studied outcomes. Endometrial thickness was significantly different between both groups; it was higher in tamoxifen group 8.9 ± 1.2 mm versus 7.2 ± 1.1 mm in clomiphene group (p -value<0.0001). Also, it was noted that there were significant statistical discrepancies between both groups regarding pregnancy rate and ongoing pregnancy rate ; as they were 22.5% and 17.5 % and 5.2% and 2.6 % in group A and B, respectively, ($p < 0.05$). Mean number of mature follicles ≥ 18 mm was statistically insignificantly, it was 1.7 ± 0.6 and 1.9 ± 0.8 in group A and group B, respectively, ($p = 0.2$).

Table 2. Outcome measures among both groups

Characteristics	Tamoxifen group (n=40)	Clomiphene group (n=38)	p-value
Follicles ≥ 18 mm	1.7 \pm 0.6	1.9 \pm 0.8	0.2 (NS)
Endometrial thickness (mm) Mean \pm SD	8.9 \pm 1.2	7.2 \pm 1.1	<0.0001**
Pregnancy rate	9 22.5%	2 5.3%	0.03*
Ongoing pregnancy rate	7 17.5%	1 2.6%	0.03*

NS: No statistically significant difference, BMI: body mass index

*Statistically significant difference.

**Statistically highly significant difference.

DISCUSSION

In the field of reproductive medicine, endometrial thickness is one of the key factors in determining the likelihood of success in assisted reproduction^[14,15]. In the current study, it was observed that administration of tamoxifen appeared to be more advantageous for ovulation induction in cases with thin endometrium. Endometrial thickness showed marked significant difference between the studied groups, it was 8.9 ± 1.2 in tamoxifen group and 7.2 ± 1.1 mm in clomiphene citrate group ($p < 0.0001$). The women were stimulated with a lower dose of CC (50 mg) so that the antiestrogenic effect on endometrium may be reduced.

Meanwhile, no significant difference was observed between the two groups regarding number of mature follicles, it was 1.7 ± 0.6 in group A versus 1.9 ± 0.8 in group B ($P = 0.2$).

Tamoxifen, non-steroid selective oestrogen receptor modulator (SERM), has dual action as an ovarian stimulating agent and has oestrogenic stimulation effect on the lower genital tract^[16]. It blocks oestradiol-binding sites on the hypothalamic–pituitary axis and prevents the negative feedback effect of oestradiol, so increases gonadotropin secretion and stimulates ovarian follicles development^[6].

Interestingly, the present study showed highly significant differences in pregnancy rate in the group treated with tamoxifen (22.5%) when compared to clomiphene citrate group (5.3 %). It is postulated that endometrial thickness is one of the essential factors in determining the possibility of success in any assisted reproduction program^[16]. Meanwhile, at least endometrial thickness of 8 mm or more is essential for implantation, also preclinical abortions increased markedly in patients whose endometrial thickness was less than 8 mm on the day of HCG administration^[17].

Tamoxifen has beneficial estrogenic stimulatory effect on the endometrium as it improved the endometrial thickness as well as the endometrial function and receptive capacity due to increased glycogen content of the endometrial tissue at the mid luteal phase in the tamoxifen cycle when compared to endometrial tissue in the non-treatment cycle^[7]; so improvement of the endometrial environment for embryo implantation could also explain the higher rate of pregnancy in tamoxifen treated group.

Published literature has reported ovulation rate of 50%-90% and pregnancy rate of 30%-50% following tamoxifen^[18]. Tamoxifen unlike clomiphene citrate

acts as an agonist on the endometrium and cervical mucus^[18]. Hence, it appears that tamoxifen may be an alternative drug to gonadotropins in cases with thin endometrium. Studies have observed that women having thin endometrium with clomiphene citrate (<7mm) exhibited improved endometrial thickness when tamoxifen was used for ovulation induction in the subsequent cycle.^[16, 19].

In a prospective observational study, 502 women with thin endometrium received different agents for induction of ovulation before intra-uterine insemination. They were randomly classified into three groups; clomiphene citrate group, tamoxifen group and continuous urine-derived follicle-stimulating hormone group. It was reported that pregnancy and livebirth rate were significantly higher ($P < 0.004$) in tamoxifen and gonadotropin groups compared to clomiphene ; while the number of follicles in the tamoxifen group was lower ($P < 0.001$) compared to other two groups^[20].

A previous study compared the efficacy of tamoxifen with that of clomiphene citrate for ovulation induction in anovulatory women and confirmed the similarity of ovulation and pregnancy rates in both groups^[6]. Another study has suggested that tamoxifen may be superior to CC as it does not appear to have an adverse effect on the endometrium. The increased oestrogenic stimulation that has been observed with tamoxifen's action on the lower genital tract may be beneficial, especially for those suffering from an adverse response following the administration of CC^[21].

The present study showed higher pregnancy loss in clomiphene group (1/2, 50%) than tamoxifen group (2/9, 22.2%) and agreed with the study of Wang et al., 2008 who reported that there were eight (8/13, 61.5%) early pregnancy losses in the clomiphene-treated patients but only two (2/26, 7.7%) in the tamoxifen group patients with a past history of thin endometrium. Tamoxifen could effectively increase mean endometrial thickness and consequently increase the chance of successful pregnancy^[16].

CONCLUSION

The current study showed promising role of tamoxifen in cases with thin endometrium. Tamoxifen can improve endometrial thickness and livebirth rate in patients with thin endometrium.

CONFLICTS OF INTEREST

There are no conflict of Interest.

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