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Research Article

Comparison between tamoxifen and clomiphene citrate for induction of ovulation and successful conception in polycystic ovarian syndrome

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ABSTRACT

Background: Being a selective estrogen receptor inhibitor (SERM) tamoxifen may be used an alternative to clomiphene citrate for ovulation induction in women with anovulatory infertility. This study was conducted to evaluate the safety and efficacy of tamoxifen as compared to clomiphene citrate in women with primary or secondary anovulatory infertility due to Polycystic Ovarian Syndrome (PCOS).
Methods: One hundred women suffering from anovulatory infertility and attending the infertility clinic and were recruited for the study. Patients were randomized to receive either clomiphene citrate (100-150 mg) or tamoxifen treatment (40-80 mg). The ovulation was monitored from day 5 to day 9 of menstrual cycle followed up by transvaginal ultrasound from day 11 every alternate day for 10 days. Ovulation and pregnancy rates were calculated.
Results: The baseline characteristics of mean age, weight, proportion of patients with primary and secondary infertility and mean duration of infertility were comparable between both the study groups. Out of 50 patients who received clomiphene citrate, 37 showed successful ovulation (ovulation rate of 64%) and 16 patients conceived (pregnancy rate of 32%). In tamoxifen group 41 women showed successful ovulation (ovulation rate of 82%) and 18 women conceived (pregnancy rate of 36%). The difference was not significantly different ($p > 0.05$). No major adverse effects were noted in both the study groups.
Conclusions: Tamoxifen has shown comparable efficacy and safety as compared to clomiphene citrate and it can be a good alternative to clomiphene citrate in patients of primary or secondary anovulatory infertility with PCOS.

Keywords: Anovulation, Clomiphene, Induction of ovulation, Polycystic ovary syndrome, Tamoxifen

INTRODUCTION

Ovulatory dysfunction is one of the most common causes of reproductive failure in subfertile and infertile couples. The most common type of ovulatory dysfunction is anovulation. Polycystic ovarian syndrome (PCOS) is thought to be the commonest cause of anovulatory infertility.[1]

Various medications are used for induction of ovulation among infertile patients with PCOS. The first line oral treatment is non-steroidal selective estrogen receptor modulators (SERM). The structural similarity to estrogen allows SERMs to bind to estrogen receptors(ER) throughout the reproductive system; however, in contrast to estrogen, SERMs binds nuclear ER for an extended period of time, which consequently depletes ER concentrations by interfering with the normal process of ER replenishment. Clomiphene citrate and tamoxifen are commonly used SERMs to induce ovulation.[2]

In the clinical setting of anovulation, SERM are thought to act primarily by binding with estrogen receptors at the hypothalamus. The competitive inhibition results in a perceived drop in endogenous estrogen levels. Depletion

of hypothalamic ER prevents correct interpretation of circulating estrogen levels which is perceived falsely as low. Such misinterpreted reduced levels of estrogen negative feedback lead to normal compensatory mechanisms. This alters the pattern of pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion to stimulate increased secretion of pituitary gonadotropins that, in turn, serve to drive ovarian follicular activity. In anovulatory women with PCOS, in whom the GnRH pulse frequency is already abnormally high, SERMs treatment was found to increases pulse amplitude, but not frequency.[3,4]

Since its introduction in 1956, clomiphene citrate has been the first-line method of ovulation induction in couples with anovulatory infertility. Many studies have shown that approximately 80% of women ovulate while using clomiphene citrate but only 40% of women achieve pregnancy. Many authors have proposed that this discrepancy in ovulation and pregnancy rate is due to the antiestrogenic effects of clomiphene, especially on the uterus, cervix and vagina, resulting in a thin endometrial lining and poor cervical mucus. Apart from serious side effects like ovarian hyperstimulation syndrome, studies have reported concerns that use of clomiphene citrate is associated with increased chances of ovarian cancer.[5,6]

Recently another SERM, tamoxifen, has also been used to induce ovulation. It is primarily used as an adjuvant therapy in the treatment of breast cancer but its use as an ovulatory agent was first reported in 1973.[7]

Unlike clomiphene, tamoxifen acts as an agonist on the estrogen receptors of the vaginal mucosa and endometrium but studies on the effects of tamoxifen on cervical mucus have been inconclusive. Also there are no reports of increased chances of ovarian cancer with use of tamoxifen. Even though its use has been shown to increase risk for endometrial cancer but with short term use that possibility is unlikely. Various randomized controlled trials found that tamoxifen is as effective as clomiphene citrate in inducing ovulation. Despite a trend toward improved pregnancy rates with tamoxifen, further studies are necessary to confirm its efficiency and safety.[8]

This prospective randomized trial was planned to find out the safety and efficacy of tamoxifen in patients of PCOS with primary or secondary anovulatory infertility.

METHODS

The proposed study was carried out at Department of Obstetrics and Gynecology, Hawler center for infertility and IVF, Erbil, Kurdistan, Iraq. The study started after obtaining permission from the Institutional Ethics Committee. Before recruiting patients and doing any procedure, written consent was taken from all the patients. The observed data was recorded in patient information sheets.

The study population consisted of 100 patients of PCOS with primary and secondary infertility who were admitted between May 2014 and May 2015 for undergoing assisted reproduction using ovulation induction treatment. The age group selected was between 20-39 years. Patients with other concomitant medical conditions were excluded. The sample size was selected based on number of patients with PCOS which visit the hospital for infertility per year and sample size for minimal statistical requirement.

Diagnoses of anovulation and infertility were done by history and clinical examination of both partners and baseline investigations including transvaginal hystrsalpingiography in state of saline infusion sonohystrography (SHG) and seminal fluid examination.

The treatment procedures followed were as per the standard treatment protocol of department. This study was performed on 100 patients with PCOS who were randomized in two different groups. Fifty patients were given clomiphene citrate in a dose of 100-150 mg and other 50 patients received tamoxifen in a dose of 40-80 mg. This is a restrictive randomization of blocking type so that to achieve the balance between two groups. Both study drugs were started from day 5 to day 9 of cycle followed up by transvaginal ultrasound from day 11 every alternate day for 10 days. Monitoring of ovulation done by one or more of the criteria including development of dominant follicle 17mm or more followed by disappearance, reduction in the size of dominant follicle and change in the shape of it and appearance of free fluid in the pouch of Douglas. The main endpoint for study was successful ovulation and successful conception.

Statistical analysis

The continuous variable data was expressed as Mean ± standard deviation (SD) and categorical variables are presented as absolute numbers with range. The continuous variables were analyzed using unpaired t-test whereas categorical data was analyzed using Chi-Square test. The p value < 0.05 was considered significant. All statistical analysis was done using GraphPad:InStat Version 3.06.

RESULTS

The characteristics about patient demographics, inducing age, body weight, type of infertility and duration of infertility were compared between two study groups and results are summarized in Table 1. Values of age of patients, body weight and duration of infertility are expressed as Mean ± SD and values of type of infertility are expressed as proportions. The results showed that baseline characteristics in both study groups were comparable ($p > 0.05$).

Table 1: Baseline characteristics in patients of PCOS in both study groups.

Characteristics		Tamoxifen Group	Clomiphene Citrate Group	P value[c]
Age (years)[a]		28.56±4.55	28.46±5.03	0.9173
Body Wight (Kg)[a]		74.7±8.23	76.44±9.12	0.3192
Type of Infertility[b]	Primary	39	41	0.8026
	Secondary	11	9	
Duration of Infertility (years)[a]		4.27±2.28	4.31±2.20	0.9291
[a] Unpaired t test, [b] Chi-Square Test; P Value[c] < 0.05 is considered significant versus clomiphene citrate group				

The efficacy of both the treatment groups was compared with respect to number of patients with successful ovulation and number of patients with successful conception. The results are presented in Table 2. Out of 50 patients who received clomiphene citrate, 37 showed successful ovulation (ovulation rate of 64%) and 16 patients conceived (pregnancy rate of 32%). In tamoxifen group 41 women showed successful ovulation (ovulation rate of 82%) and 18 women conceived (pregnancy rate of 36%). Tamoxifen treated group showed comparable efficacy as compared to clomiphene citrate treated group (P > 0.05). The safety of patients was evaluated by observing adverse events. Both study groups did not show any significant adverse events.

Table 2: Comparison of successful ovulation and pregnancy in both study groups.

Characteristics		Clomiphene Citrate Group	Tamoxifen Group	P value
Ovulation Induction	Yes	37	41	0.4689
	No	13	9	
Pregnancy	Yes	16	18	0.8328
	No	34	32	
Chi-Square Test; P value <0.05 is considered significant versus clomiphene citrate group				

DISCUSSION

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine condition that affects approximately 5% to 10% of women in the reproductive age group. Depending on the population being examined, however, prevalence rates as high as 26% have been reported. PCOS accounts for 75% of anovulatory infertility. Additionally, when pregnancies do occur, the first trimester miscarriage rate is as high as 30% to 50%.[9]

The study showed that tamoxifen is equally beneficial in inducing ovulation and helps in successful conception as compared to clomiphene citrate. Clomiphene citrate was introduced 40 years ago and still it is one of the most commonly used agents in ovulation induction. However, one major limiting factor with use of clomiphene citrate is that the pregnancy rates (30-40%) are not as good as ovulation rates (70-80%). It was concluded by many previous trials that lack of conception despite evidence of ovulation may be due to antiestrogenic effects of clomiphene citrate on the endometrium, which may manifest as a thin endometrium. With this, it was initially theorized that tamoxifen's estrogenic effects on the endometrium and cervical mucus would result in higher pregnancy rates. Both SERM were equally effective in inducing ovulation. The ovulation rates were high in both groups; however, pregnancy rates were much lower. Although the proportion of patients getting pregnant were higher after ovulation with tamoxifen, this finding was not statistically significant when compared with clomiphene citrate treated group.

SERM are used apart from diet and lifestyle modification in management of infertility in patients of PCOS. Obese women with PCOS often do not respond to clomiphene, with only a 20% ovulation rate at the 50 mg dose seen in women weighing > 91 kg.[10]

Gonadotrophins have been used as the next choice but these are very expensive, the complication rate is high and they need close supervision and monitoring.[11]

A recently published metaanalysis concluded that CC and tamoxifen are equally effective in inducing ovulation and similar finding was seen in our study.[8]

Various studies have shown similar finding regarding ovulation and pregnancy rate due to use of tamoxifen. The doses used were also between 40-80 mg. A study by

Williamson et al reported an ovulation rate of 81% whereas another study by Messinis et al reported the ovulation rate as 76.08% while using tamoxifen for ovulation induction.[7,12] The pregnancy rates as seen in our study were found to be similar to those reported by Williamson et al. and Fukushima et al., (35.5%) with the use of tamoxifen in cases of luteal phase defects. In patients of PCOS Gulekli et al reported an ovulation rate of 70% whereas Seyedoshohadaei F et al reported ovulation rate of 68% and pregnancy rate of 40%.[13-15]

Tamoxifen used for a short duration does not appear to be associated with an increased risk of ovarian or endometrial cancer. The present prospective study was conducted to find out the ovulation and pregnancy rates with different doses (40 mg and 80 mg) of tamoxifen in women with anovulatory infertility.

The present study has shown that tamoxifen is a good ovulation-inducing agent and is devoid of side-effects and complications in patient of PCOS with anovulation. However the efficacy found was comparable to clomiphene citrate treated patients of PCOS. Therefore tamoxifen can be used as an alternative to clomiphene citrate in management of anovulation and infertility in patients of PCOS. Further studies are needed to validate the results.

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