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Comparison of tamoxifene v/s clomiphene citrate in ovulation induction

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Abstract

Introduction: Being a selective estrogen receptor inhibitor (SERM) tamoxifen may be used as 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.

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 (50 mg) or tamoxifen treatment (40 mg). The ovulation was monitored from day 3 to day 7 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, and mean duration of infertility were comparable between both the study groups. Out of 100 patients who received clomiphene citrate, 51 showed successful ovulation (ovulation rate of 45.94%) and 5 patients conceived (pregnancy rate of 10%). In tamoxifen group 67 women showed successful ovulation (ovulation rate of 59.82%) and 9 women conceived (pregnancy rate of 18%). The difference was 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.

Keywords: Anovulation, clomiphene, induction of ovulation, tamoxifen

Introduction

Ovulation is the central event in the reproductive cycle. Ovulatory disorders account for 20-25% of all cases of infertility [1].

Ovulatory dysfunction is one of the most common causes of reproductive failure in subfertile and infertile couples.

Ovulation Induction refers to the therapeutic restoration of the release of one egg per cycle in the woman who either has not been ovulating regularly or has not been ovulating at all. Although it is usually acceptable for OI to result in the release of two eggs, one should avoid the ovulation of more than two eggs in an effort to minimize the risk of OHSS and multiple gestation.

Once ovulation has been documented for a particular treatment. Patients should be mentally prepared to continue with that regimen for at least 3 cycles. Because for most treatment the rate of a pregnancy occurring per therapeutic cycle is the same for each of the first three cycles.

Various medications are used for induction of ovulation among infertile patients with PCOS [2]. 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

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increased secretion of pituitary gonadotropins that, in turn, serve to drive ovarian follicular activity [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 primary or secondary anovulatory infertility.

Methods

The proposed study was carried out at Department of Obstetrics and Gynecology, C.U. Shah medical college, Surendra nagar. 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 primary and secondary infertility who were admitted between May 2014 and May 2015 for 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 primary and secondary infertility, 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 and seminal fluid examination.

The treatment procedures followed were as per the standard treatment protocol of department. This study was performed on 100 patients who were randomized in two different groups. Fifty patients were given clomiphene citrate in a dose of 50 mg and other 50 patients received tamoxifen in a dose of 40 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 3 to day 7 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 17 mm 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

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). Quantitative variables such as age and body mass index (BMI), were categorized as per standard criteria and were expressed as mean and standard deviation.

Values of age of patients, body weight and duration of infertility are expressed as Mean \pm SD.

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. Statistical significance was considered at p value less than 0.05.

Results

The characteristics about patient demographics, including 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 \pm SD and values of type of infertility are expressed as proportions.

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

Characteristics (mean)		Tamoxifen group	Clomiphene citrate group
Age (years)		25.96	26.72
BMI		22.54	22.75
Types of infertility	Primary	41	37
	Secondary	9	13
Duration of infertility (years)		2.44	2.43

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 111 cycles treated with clomiphene

citrate, 51 showed successful ovulation (ovulation rate of 45.94%) and 5 patients conceived.

In tamoxifen group out of 112 cycles 67 women showed successful ovulation (ovulation rate of 59.82%) and 9 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 groups didn't show any adverse effects

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

Characteristics		Clomiphene citrate group (n=111) ^a	Tamoxifen group (n=112) ^a	P value
Ovulation Induction	yes	51	67	0.0379
	no	60	45	
Pregnancy	yes	5	9	0.0463
	no	45	41	

a = number of cycles treated with clomiphene or tamoxifen, mann Whitney test; p value <0.05 is statistical significant.

Discussion

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^[9, 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].

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 Seyedshohadaei F *et al.* reported ovulation rate of 68% and pregnancy rate of 40%^[12, 14].

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.

References

- Rowland M. Infertility therapy, Effect of innovations and increasing experience. *J Reprod Med.* 1980; 25:42-55.
- Jonathan S. Berek and Novak's textbook of gynecology. 15th edition Williams & Wilkins. 2002; 25:840-852.
- Hamilton-Fairley D, Kiddy D, Watson H, Paterson C, Franks S. Association of moderate obesity with poor pregnancy outcome in women with polycystic ovary syndrome. *Br J Obstet Gynaecol.* 1999; 99:128-131.
- Speroff L, Fritz M. Clinical gynaecologic endocrinology and infertility. 8th ed. Baltimore: Lippincott Williams and Wilkins. 2011, 1137-1190.
- Eden JA, Place J, Carter GD, Jones J, Alaghband Zadeh, Pawson ME *et al.* The effect of clomiphene citrate on follicular phase increase in endometrial thickness and uterine volume. 1989; 73:187-90.
- Whittemore AS, Harris R, Ignore J *et al.* Characteristics relating to ovarian risk: Collaborative analysis of 12 US case-control studies. *Am J Epidemiol.* 1992; 136:1184
- Williamson JG, Ellis JD. The induction of ovulation by tamoxifen. *J Obstet Gynaecol Br Comwlth.* 1973; 80:844-7.
- Steiner AZ, Terplan M, Paulson RJ. Comparison of tamoxifen and clomiphene citrate for ovulation induction: a meta-analysis. *Hum Reprod.* 2005; 20(6):1511-5.
- Greenblatt RB, Barfield WE, Jungck EC, Ray AW. Induction of ovulation with MRL, 41. Preliminary report. *Journal of the American Medical Association.* 1961; 178:101-104.
- Adashi EY. Clomiphene citrate: mechanism(s) and site(s) of action – a hypothesis revisited. *Fertility and Sterility* 42, 331-344.
- Wu CH. A practical approach to clomiphene therapy. *Clin Obstet Gynecol.* 1984; 27:953-65.
- Fukushima T, Choshin T, Keizo F, Masao M. Tamoxifen in the treatment of infertility associated with luteal phase deficiency. 1982; 37:755-61.
- Gulekli B, Ozaksit G, Turhan NO, Senoz S, Oral H, Goakman O *et al.* Tamoxifen: An alternative approach in clomiphene resistant polycystic ovarian syndrome patients. *J Pak Med Assoc.* 1993; 43:89-91.
- Seyedshohadaei F, Zandvakily F, Shahgeibi S. Comparison of the effectiveness of clomiphene citrate, tamoxifen and letrozole in ovulation induction in infertility due to isolated anovulation. *Iranian Journal of Reproductive Medicine.* 2012; 10(6):531-6.