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Research Article

Comparison the Effect of Letrozole and Tomoxifin in infertile women with Clomid Citrate resistant in polycystic ovarian syndrome

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ABSTRACT

Polycystic ovary syndrome (PCOS) is the most frequent endocrine problem affect women in the reproductive age and commonest causes of hyperandrogenic anovulatory infertility. This study was aimed to evaluate the efficacy of letrozole on ovulation induction and pregnancy rate in comparison to tamoxifen in clomiphene CC-resistant PCOS patient. This prospective randomized study was included 80 patients divided into 2 equal groups, Group (1) involved 30 women who were given letrozole 2.5 mg tab orally once per day from day 5to 9 of the menstrual cycle, for 3 successive cycles. Group (2) included 30 women, had been received TMX with a dose of 20 mg per day starting from day 5 of manse to day 9 of it, for 3 successive cycles, compare the effectiveness of letrozole and tamoxifen in management of clomiphene citrate resistance PCOS patients, during of 15th August 2015 to 15th of December 2016 and was performed infertility clinics of AL-Batool teaching hospital. The results of this study revealed that Letrozole is better than tamoxifen in producing acceptable follicular diameter, endometrial thickness and pregnancy rate in women with the clomiphene-resistant polycystic ovarian syndrome. With pregnancy rate of (12%) in tamoxifen group versus (27%) in letrozole group. Letrozole is effective, an available drug that is superior to tamoxifen as ovulation induction agent in clomiphene-resistant polycystic ovarian syndrome.

Keywords: Clomiphene resistance; Polycystic ovarian syndrome; Ovulation induction; Tamoxifen; Letrozole.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most frequent endocrine & medical complaint in infertile women, affects approximately 4 to 12 percent of women of productive age (Teede et al., 2010) and is detected in approximately 75 percent of cases of anovulatory Infertility (Sirmans and Pate, 2013). Considerate the main reasons of Infertility and choosing a suitable treatment plan is a diagnostic &therapeutic priority (Lee, 2001; Moslemizadeh et al., 2008). Ovarian stimulations stay the cornerstone of attaining a good ovulatory response and a positive clinical result following assisted reproduction, Successful treatment of anovulation is one of the greatest advances in Infertility managing. The drugs used have an important role in influencing the outcome of treatment ("Use of clomiphene citrate in infertile women: A committee opinion," 2013). Clomiphene citrate (CC) is the first common oral pharmacologic drug has been used to prompt ovulation in these women, but some women fail to conceive with this therapy, likely due to the anti-estrogenic action of CC on the endometrium or its intervention with the corpus luteum function (Badawy et al., 2008).Other infertility treatments may be recommended if clomiphene treatment is not successful; these include the use of aromatase inhibitor (Thessaloniki et al., 2008), insulin-sensitizing agent and surgery (Borenstein et al., 1989).

Tamoxifen (TMX) is a diphenylethylene derivative, another anti-estrogenic agent which is like to CC in structure has been considered for ovulation dysfunction treatment. With restricted literature on the practice by using of TX for ovulation induction, ovulation rates and pregnancy rates have been reported as 50-90%, 30-50% respectively (Badawy et al., 2006; Nafee and Metwally, 2014).Tamoxifen has revealed acceptable results in CC failure cases too (Badawy et al., 2008). The improved in ovulation and pregnancy rates are likely because of a higher score of cervical mucus &improved the corpus 1uteum function (Fisher et al., 2002) infertile women who are not responding to anti-estrogens agents may require a different treatment. Aromatase inhibitors (AI), aromatase is a cytochrome P-450 hemoprotein enzyme is responsible for the conversion of androgen to estrogen. (AI) block estrogen production, so the use of aromatase inhibitors may be useful in PCOS women who are resistant to anti-estrogen (Al-Fadhli et al., 2006). Letrozole, a potent, non-steroidal selective reversible aromatase inhibitor, it could be used for ovulation with obvious lack of anti-estrogen adverse outcome as thin endometrium and poor cervical mucus due to its half-

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life is shorter than clomiphene, so pregnancy rate is improved (Azziz et al., 2004; Brown et al., 2009).This study has been formed to determine & compare the efficiency of Tamo xifen (TX) compared to letrozole for inducing ovulation & achieving pregnancy in CC –resistance women with PCOS.

PATIENTS AND METHODS

This prospective study was done during the period from15th August 2015 to 15th of December 2016, attending the infertility clinic in AL-Batool Teaching Hospital. This study was carried out on 80 CC-resistant, their age are from (20 to 35) years were enrolled, seeking pregnancy and they were diagnosed as PCOS, established on the Rotterdam criteria (15) which must exhibit being there of two of three criteria, i.e.oligomenorrhea and/or anovulation, clinical and/or biochemical signs of hyperandrogenism, and/or polycystic ovaries on ultrasound.

All patients receiving 150 mg of a CC per day for 5 days, for three cycles at least previously. but without successful stimulation of ovulation. Informed permission was obtained from all participants with full history –taking, a clinical examination including a pelvic examination were done and a full investigation had been done including: 1) a complete hormonal report, including follicle-stimulating hormone, luteinizing hormone, prolactin, thyroid stimulating hormone, estradiol, and free testosterone (day 2-3of the cycle) 2) ultrasound of pelvic to show polycystic changes in the ovary (ovaries with at least 10 subcapsular cysts 2-10 mm in diameter) and exclusion of any other pelvic anomalies. 3) hysterosalpingography to assess tubal patency. 4) semen fluid analysis of male partner. Exclusion criteria include 1) infertility due to other causes of uterine &tubal pathologies. 2) mal factor (detective semen)3) any medical disease that can affect fertility like diabetes mellitus, thyroid disease. 3) history of the pelvic inflammatory process and /or having abnormal laboratory results other than PCOS features.

They were then divided into two groups

Group (1) involved 30 women who were given letrozole (Femara, Novartis,)2.5 mg tab orally once per day from day 5to 9 of the menstrual cycle, for 3 successive cycles. Group (2) included 30 women, had been received TMX with a dose of 20 mg per day starting from day 5 of manse to day 9 of it, for 3 successive cycles. Serial transvaginal ultrasonographic follow-up was performed for each case for revealing of ovulation, beginning from day 10 of the menstrual cycle and every other day, with measurement of number &size of follicles and endometrial thickness. Human chorionic gonadotrophin10,000 IU was given intramuscularly, to trigger ovulation when at least one mature follicle >18 mm diameter was noticed.

Statistical analysis

Those data expressed as mean plus minus standard deviation was used an unpaired t-test to show the comparison between groups, while those express as frequency and percentage, the comparison done by Fisher exact test.

RESULTS

A total of 80 PCOS women seeking pregnancy were enrolled in this study. The demographic data are presented in table 1 showed no significant differences in all parameters.

Table 1: Comparison of demographic data between the two study groups by unpaired t-test

Parameters	Tamoxifen (N=40) Mean +SEM	Letrozole (N=40) Mean± SEM	P Value
Age (Yr.)	29.97 ± 0.81	29.75 ± 0.85	NS(0.456)
Weight (Kg)	70.65 ±1.49	69.55 ±1.69	NS(0.628)
Duration of Infertility In Year	2.10 ±0.87	2.19 ±0.093	NS(0.717)
BMI(Kg/m^2)	26.63 ±0.62	26.94 ±0.56	NS(0.520)
FSH	4.42 ±0.19	4.24 ±0.17	NS(0.512)
LH	7.52 ±0.38	7.64 ±0.38	NS(0.234)

Table 2: Comparison of diameter of follicle at day 13 of 3 cycles between the two study groups by unpaired t-test

Diameter Of Follicle (mm)		Tamoxifen(N=40) Mean ±SEM	Letrozole (N=40) Mean ±SEM	P Value
Cycle 1	day 10	11.27 ±0.32	16.17±0.10	0.020
	day 12	13.12 ±0.24	17.67±0.10	0.034
	day 14	15.27 ±0.23	19.30±0.18	0.015
Cycle 2	day 10	12.33 ±0.29	16.30 ± 0.14	0.023
	day 12	14.71 ±0.23	17.75 ± 0.09	0.001
	day 14	16.53 ±0.21	20.10 ±0.19	0.018
Cycle 2	day 10	12.84 ± 0.27	16.06 ±0.21	0.087
	day 12	15.61 ±0.26	17.70 ±0.11	0.030
	day 14	17.64 ±0.27	20.46 ±0.24	0.067

Table 3: Comparison of endometrial thickness and pregnancy rate between tamoxifen and letrozole group by Fisher exact test

Group	Cycle1 Mean±SEM	Cycle2Mean±SEM	Cycle3Mean±SEM	Follicular Size≥18 No.(%)	Pregnancy Rate No.(%)	Endometrial Thickness Mean ±Sem
Tamoxifen(N=40) Mean ±SEM	13.22±0.21	14.54±0.21	15.38±0.23	41(11.4)	12(30.0)	5.85 ± 0.14
Letrozole (N=40) Mean ±SEM	17.71±0.14	18.12±0.16	18.14±0.22	102(27.8)	27(67.5)	9.85 ±0.14
P value	0.017	0.023	0.015	0.033	0.0005	0.002

Table 4: Comparison of pregnancy rate between primary and secondary infertility by Fisher exact test

Type of infertility	Tamoxifen	Letrozole	P Value
Primary	13/24	12/22	NS
Secondary	5/16	7/18	

Regarding the diameter of the dominant follicle, it was significantly higher in day 10,12, and 14 of the cycle in patients who received letrozole than in patients received tamoxifen with a p-value of <0.005 as shown in table 2. Both endometrial thickness and pregnancy rate were higher in Letrozole group than in tamoxifen with a p-value of <0.001 for endometrial thickness and 0.0005 for pregnancy rate as in table 3. With regards to the type of infertility (primary or secondary), there was no significant difference in pregnancy rate in both groups with a p-value of 0.063 as shown in table 4.

DISCUSSION

In present study the reproductive outcome of women with Cc resistance pgs was compared after using either letrozole or tamoxifen and it was shown that letrozole is better than tamoxifen in achieving acceptable diameter of mature follicles, this agrees with a number of studies (Abdellah, 2011; Holzer et al., 2006; Casper and Mitwally, 2011; M.N. et al., 2015); in all these studies letrozole achieve acceptable, limited numbers of mature follicle with no adverse effect on endometrium or cervix. This can be explained by the fact that letrozole is an aromatase inhibitor, which will suppress estrogen production in both ovaries and brain, so gonadotrophin release will be increased by negative feedback of estrogen leading to stimulation of ovarian follicles. Additionally, letrozoleacts locally on ovaries to increase follicular sensitivity to FSH by increasing the local androgen in the ovaries as the conversion of androgen to estrogen is inhibited. In contrast, Sharma et al. (2014) found that letrozole and tamoxifen are similar in term of ovulation rate. This may be due to a different study design and regime as it compares the effect of tamoxifen and letrozole on PCOS women in general, not a cc-resistant PCOS. Regarding endometrial thickness, it was better in letrozole group. These findings agree with the several studies (Mitwally and Casper, 2001; Baran et al., 2010; Zeinalzadeh et al., 2010; Dakhil, 2017).This effect of letrozole on endometrial thickness is explained by the fact that it has no anti-estrogen effect as it does not cause estrogen receptor downregulation in addition to its short half-life of about 40 – 45 hours. Pregnancy rate was also higher in letrozole group, this agrees with M.N. et al. (2015) and Alsereah (2015). They found that the better follicular size thicker endometrial thickness in letrozole group results in higher pregnancy rate compared to tamoxifen, in addition, letrozole has a short half-life of about 40-45 hours.

CONCLUSION

Letrozole is effective, an available drug that is superior to tamoxifen as ovulation induction agent in clomiphene-resistant polycystic ovarian syndrome.

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