Original paper

Comparison between The Efficacy of Combined Metformin – Letrazole with Metformin – Clomiphene Citrate in Polycystic Ovarian Syndrome

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Abstract

Background: Adding Metformin to clomiphene citrate in clomiphene –resistant PCOS patients increases ovulatory response. However because of anti-estrogenic effects of clomiphene it may be associated with lower pregnancy rate. Offsetting the ovulation rate benefit, Letrazole is an aromatase inhibitor which induce ovulation without antiestogenic effects.

Aim of Study: is to induce ovulation& increase the pregnancy rate and live birth rate in patient with PCOS using a new era of therapy with less side effects, less complications and better patient compliance.

Materials and Methods: The study is a single – blind randomized clinical trial , 120 ovarian cycle were studied in 60 clomiphene – resistant patients with PCOS , who were chosen among 115 PCOS patients attending infertility clinic in Samawa city – Iraq during the years 2011 – 2012 Infertile women with PCOS were randomly divided into Metformin –Letrazole (29 patients) and Metformin – clomiphene groups (30 patients) after an initial 6 – 8 weeks of metformin.They received either Letrazole (5mg) from2nd to 7th day orclomiphene citrate (100mg)daily from 5th to 9th day of menstrualcycle . Estradiol (E2) level , number of follicles and endometrial thickness were measured on the day of HCG administration .The pregnancy rate of both groups also estimated.

Results: Mean total E2 and E2per mature follicle were significantly higher in clomiphene group without a difference in mean number of follicles ≥ 18mm and ovulation rate .

Endometrialthickness was significantly higher in Letrazole group .Thepregnancy rate in Letrazole group (10 patients, 34.50%) as compared with clomiphene group (5 patients 16.6%) did not show significant difference, whereas full – termpregnancies were higher in Letrazole group (10 patients 34.5%) versus 3 patients (10%).

Conclusion: In clomiphene resistant PCOS, the combination of Letrazole and Metformin leads to higher full term pregnanciesas compared with clomiphene and Metformin .

key words: Clomiphene citrate, Letrazole, Metformin, PCOS, pregnancy rate.

Introduction

Infertility has been attributed to various factors, amongst which anovulation is the cause of about 40% of all female infertilities. Polycystic ovarian syndrome (PCOS) is the major cause of anovulation[(1)], the incidence of which has been reported to reach 6% in infertile females[(2)]. Polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders in women of childbearing age. Although it is a major cause of infertility due to chronic an

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ovulation, its etiology remains unknown and its treatment is difficult. However, most symptoms of PCOS can be adequately controlled or eliminated with proper diagnosis and treatment. Therefore, treatment modalities and ovulation induction protocols must be balanced for optimal results [(1)].

Antiestogenic drugs, such as, clomiphene-citrate, as the first line therapy for ovulation induction in these patients and are capable of producing ovulation in in 70–75% of cases. Satisfactory response is seen in 70% of patients when clomiphene citrate is given at a dosage of 50 – 100 mg/day. If patients fail to respond to a dosage of 150 mg/day and the endometrial thickness below 6 mm. they considered as clomiphene resistant[(1)].

Animal studies show that a high dose of clomiphene citrate has adverseeffects on fertility and the initial stages of fetal growth and, though not proven in human studies [(3)] .

In addition, studies has shown a significant difference between rates of ovulation and pregnancy and a higherabortion rates in patients undergoing clomiphene-citratetherapy. Thus, the use of a simples oral drug, as a safe alternative to clomiphene citrate, can produce a new horizon in ovulation induction. Letrazole is a newly designed third generation selective aromatase inhibitor (acts by reversibly inhibiting the enzyme responsible for estrogen biosynthesis by decreasingestrogen level in the body, Letrazole stimulates the hypothalamus and/ or pituitary gland from the negative feedback of estrogen. This result in increased level of endogenous follicular Stimulating hormone and luteinizing hormone, which stimulates ovarian follicular development [(2)] . With the above characteristics, it can be used to induce ovulation in infertile women with PCOS[(3)].

The half-life of Letrazol is about 2 days . This means that it takes about 2 days for the drug concentration to drop in one – half in the serum. In general, a drug will be completely eliminated in 5 half-lives. In the case of letrazoel, this is about 10 days. The pharmacokinetic studies which determined the half-life of the drug may not has been done in woman of reproductive age as the drug was to be used in post-menopausal woman. This it may be metabolized differently in younger women. In fact, two unknown meteorites are metabolites in the PDR which may have unknown biological activity.

The clearance of drug is slow and the volume distribution is approximately 2L/kg indicating that it is widely distributed in the body (2), (3) this raises the possibility that the drug or its metabolites could be distributed to the ovary or uterus organs vital for reproduction .

Previous studies has shown the beneficial effects of metformin in PCOSpatients by improving pregnancy rate and the metabolic situation and by decreasing the complications of pregnancy such as gestational diabetes (4) .

In addition, the beneficial effects of combined metformin–clomiphene therapy has also been reported in clomiphene–resistant PCOS patients (5)

Studies has also been performed concerning the beneficial role of letrazole in clomiphene–resistant patients(6). However, no studies has yet compared the effects of complained metformin–letrazole therapy with those of metformin–clomiphene citrate. The aim of this study was to compare and determine the efficacy of combined metformin-etrazole administration to that of metformin–clomiphene citrate in clomiphene citrate in infertile woman with PCOS.

Material & Methods

In this Single–blind randomized clinical trial, 120 ovarian cycle were studied in 60

clomiphene–resistant patients with PCOS, who were chosen among 115 PCOS patients attending infertility clinic in Samawa city–Iraq during the years 2011–2012. The majorcriteria for diagnosis of PCOS were oligo–and or anovulation, clinical or biochemical signs of hyper and organism and polycystic ovaries which is in accord with the revised 2003 Rotterdam criteria of PCOS.

Thyroid function, prolactin level, hysterosalpingeography and husband sperm analysis were checked for normal values. Inclusion criteri a were consisting of PCOS patients who had failed to became pregnant after three courses of 150 m clomiphene citrate (consider as clomiphene – resistant), where are true value of the above mentioned tests were normal .

Exclusion criteria including patients withhistory of liver and kidney failure, cardiovascular disease , diabetes (based on criteria set by the American Diabetic Associations) or patients who consumed metformin or drug affecting insulin secretion or clomiphene citrate in the previous months . The patients were visited and examined by gynecologist and sonographists .A series of blind envelopes numbered from 1 to 60 has been prepared. Each patients was invited to pull out an envelope and was placed by the clinical secretory in either metformin – letrazole group (Group A) or Metformin – clomiphene citrates group (Group B) . ®

All patients of bottom groups received 1500mg Metformin (Glucophage) a day (500 mg three times a day) for 6-8 weeks. If pregnancy occurred, the patients was excluded from the study. However, in case of failure of pregnancy after the end of this period, the patients in the Metformin–clomiphene group (Group B) were given 100mg clomiphene citrate (clomid, sonafiaventis) for 5days starting from day 5 of their menstrual cycle, and those in the metformin–letrazole group (Group A) received 5mg letrazole (Femra, Novartis) from day 3 of their M.C. for 5 days.

The condition of the ovaries was determined by transvaginal sonography every other day from day 12 of the cycle by a single sonagraphist (according to the length of previous cycles). A total of 10000 Iu of HCG was administered to those in whose at least one ovarian follicle size $\geq$ 18 m in size. Estrodial (E2) level and the ratio of E2 to number of mature follicle were determined on the day of HCG administration. The patients were advised to has intercourse every other day from3 daysbefore to 5 days after ovulation (fertile window). In order to confirm ovulation, transvaginal sonography was performed. In case of delayed menstruation in a patient who had ovulated, After ovulation B – HCG was measured, and pregnancy was observed by trans vaginal sonography. In case of pregnancy and observation of fetal heart rate , metformin was discontinued, and in case of therapeutic failure(negative B-HCG), the patients was advised to continue metformin and to participates in there courses of therapy .

The statisticians, sonogrophist and gynaecologisti involved in this trial were blind to the kind of treatment whereas patients were not blind to the kind of letrazole and clomiphene tablet , because of their known different shapes. S PSS version 22.0 software was used for statistical analysis and the t – test and chi – square tests were used as appropriate. p – values less than 0.05 were considered as statistically significant .

Results

On the whole, 120 ovarian cycles were studied in 59 patients {53 cycle in 29 patients in the letrazole group (Group A) and 67 cycle in 30 patients in the clomiphene citrate group (Group B)}. After metformin administration, one of the patients in the letrazole group became

pregnant and was excluded from the study. A significant statistical difference was not observed between group A and B with respect to mean demographic variables including age , BMI and duration of infertility as shown in table -1- .

Mean total E2 and Mean E2 level per mature follicle on the day of HCG administration was significantly higher among patients in the clomiphene group as compared with those in the group A (1664 ± 1349 and 981.35 ∓64844 pM/l versus 783.38 ∓ 251.50 and 447.60 ∓ 133.36 pM / l) . The pregnancy rate between the two groups did not show significant difference : 10 patients (34.50%) as compared with 5 patients (16.67%) (p = 0.2) (TABLE -2). Two miscarriages occurred in the clomiphene citrate group in the first trimester ,whereas none – were seen in the letrazole group. Gestational age in the time of delivery in both groups was between 37 and 39 weeks, with no preterm labor . Mean birth weight was 2860 gm in group A and 2900gm in Group B, which were both lighterthan Iraq mean birth weight as it is 3100gm for girls and 3300gm for boys. There were no abnormalities in the two groups. Term pregnancies were significantly higher in the letrazole group than the clomiphene group: 10 patients (34.50%) as compound with 3 patients (10%) (p=0.045). The rate of pregnancy in the cycle was 7% (5 of 67 cycles) in the clomiphene group and 19% (10 of 53 cycles) in the letrazole group which was not statistically significant (p= 0.06) as shown in (FIGURE 2).

Table 1. Demographical variation of Group A (Letrazolet group) & Group B (Clomiphene citrate group)

Parameters	Group A	Group B
1- Mean age (years)	29.61	30.76
2- Mean BMI (kg/m2)	30.22	32.15
3- Duration of infertility (months)	56.3	64.1

Table 2. The compassion of Group A and Group B regarding hormonal and ultrasonic parameters

Parameters	Group A	Group B
1- Mean number of mature follicles	4.4	6.8
2- Mean total E2 (pM/ L)	1664.5	783.8
3- Mean E2 / mature follicle	981	447
4- Mean ultrasonic reports in fertile window	3.7	4.2
5- Mean endometrial thickness at time of HCG administration	9.27	8.15
6- Ovulation rate	67.5 %	70.9 %

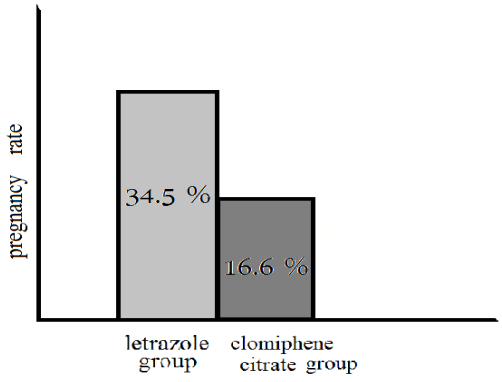

Figure 1. Pregnancy rate in Letrazole Group and clomiphene citrate group in PCOS Patient

Discussion

The results of this study indicate that women with PCOS experience higher pregnancy rates and fewer abortions when they receive combined metformin–Latrazolein compassion with Metformin–clomiphene. No significant relationship between age, BMI or duration of infertility in the clomiphene citrate or the letrazole group was observed According to the result of this study, mean endometrial thickness on the day of HCG administration was significantly less in subjects taking clomiphene citrate than those who received letrazole (0.55 ∓0.28 rersus 0.22∓0.13 cm), which is similar to the result achieved by Mitwally et al (2005). However in the study performed by Al – Fozan et al (2004), a significant relationship was not found between their two groups. It is probable that the cause of endometrial thickening in patients receiving letrazole is because of improved vascularization as compound with clomiphene citrates[4].

Other studies also show that clomiphene citrate can cause inadequate endometrial thickness in 15 – 50 % of patients (Fisher et al, 2002) and has negative effects on the quality or quantity of the cervical and endometrial mucosa[7]. These complications may be attributed to the anti–estrogenic effect and the relatively longer half–life of clomiphene citrate, thus decreasing endometrial thickness by its long–term effect in decreasing the number of estrogen receptors[7].

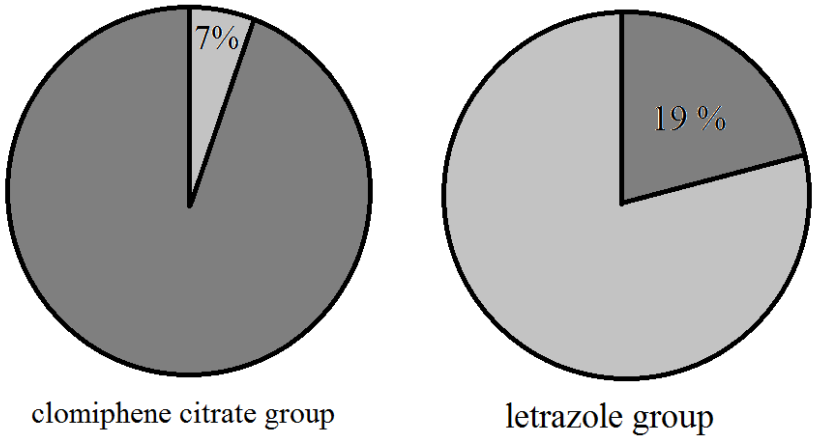

Figure 2. pregnancy rate in each menstrual cycle for both clomiphene citrate group and letrazole groupe in PCOS patient.

A significant statistical relationship did not exist between the frequency of ovulation in either group; neither was there a significant relationship between the mean number of mature ovarian follicles (diameter>18mm). In the study performed by Al–Fozan et al (2004), a significant relationship did not exist between the number of follicles measuring more than 14 and 18 mm among patients who were studied for ovulation induction and intrauterine insemination (IUI) in the two groups. However, in the study performed by mitwally et al (2005), the mean number of mature follicles was significantly higher in the letrazole group versus clomiphene citrate group. According to the findings of this study, mean total E2 and E2 level per

mature follicle were significantly higher in the clomiphene citrate group than the letrazole group on the day of HCG administration (1664.63 versus 981.38 pM/L and 783.38 versus 447.60 pM/1). High supra-physiological level of estrogen attained during ovarian stimulation with clomiphene citrate may explain some of the adverse effects of clomiphene on the outcome of infertility treatment, although reducing estrogen synthesis by aromatase inhibitor may ameliorate such deleterious effects. In the current study .those was no difference between the clomiphene citrate group and letrazole group with respect to the adverse effects of metformin .

Also, a significant relationship did not exist between the letrazole and clomiphene citrate groups in regard to pregnancy rate , although a non – significant increase in pregnancy rate was observed in patients who received letrazole (34.50 versus 16.67%); this almost two folds increase in pregnancy rate could have been significant if a larger group of patients was including. Because two abortions occurred in the clomiphene citrate group, and non in the letrazol group, full term pregnancy were significantly higher in the latter was compared with former group. All newborn in both groups were healthy without any abnormality.

The study performed by Mitwally and Casper (2001), which assessed the effect of letrazol administration in 10 women with PCOS, showed that pregnancy occurred in a 20% of cases. Sammour et al, (2001), also studied the efficacy of letrazole and clomiphene citrate in 49 women with idiopathic infertility , also showed pregnancy rate to be higher in patients receiving letrazole than those receiving clomiphene citrate (16.7 resus 5.6%). As seen in both studies, pregnancy rate is higher in patients receiving letrazole than those receiving clomiphene – citrate but is lower when compared with the current study. Thus, we may speculate that the combination of Metformin–letrazol is better than letrazole alone, particularly in overweight women who has more intense anovulatory state with higher androgen level producing more resistant hypothalamic pituitary ovarian axis . Further studies are required for this hypothesis to be confirmed .

In the study performed by Al- Fozan et al (2004). pregnancy rate 11.5% in the letrazo; e and 8.9% in the clomiphene citrate groups, which was not statistically significant.

According to result derived from the current study as well as previousones , it seems that the risk of miscarriage is higher than expected in the clomiphene group which may be because of changes in peripheral estrogen level in the cervical and endometrial mucosa. clomid citrate accumulation during pregnancy and the initial stages of development in mouse and rabbit but has not been proven in other studies [8] Hypotheses have been stated concerning the direct adverse effects of clomiphene citrate on oocytes, but view are variable. One of the probable causes of the low success rate of clomiphene citrate is inadequate uterine blood flow during the early luteal phase and the stage of implantation [8], Finally, there are difficulties in ovulation in women with oligomenorrhea and PCOS, which may be because of insulin resistant and its related factors [5]. It is strongly believed that high serum insulin level is related to PCOS pathogenesis. Metformin is an effective drug in diabetes and can increase tissue sensitivity to insulin as well as decrease plasma insulin level and hepatic glucose production. In PCOS patients, metformin can decrease the level of LH – and ovarian androgen level as well as correct hyper insulin anemia[6]. The effect of metformin on the activity of ovaries has been shown in clinical trials[5] and has been shown to correct irregular menses by producing ovulation [11]. In addition,

Nestler et al, (1998) showed that metformin increases ovarian response to clomiphene citrate in obese women with PCOS. According to this finding, the current study was normal in that who used metformin simultaneously with clomiphene and letrazole. Aromatase is the enzyme necessary for converting and rostencdione to estrogen and finally to E2 in peripheral tissues [(2)]. Aromatase inhibitors can prevent-peripheral estrogen production in patients in whom peripheral estrogen secretion is increased [(2)]. These drugs have high potency and estrogen level can be controlled by 97 – 99% at a dosage of 1 – 5 mg / day with the same mechanism, selective aromatase inhibitors such as letrazole are used to induce ovulation especially in infertile women with PCOS [(8)].

The use of aromatic inhibitors in the initial follicular phase has a negative feedback effect on the hypothalamus and pituitary glands thereby causing GnRH LH and FSH secretion with resultant ovarian follicular growth stimulation. They may also have direct action on the ovaries and increase follicular sensitivity to FSH. Women with PCOS may also have relatively low levels of ovarian aromatase, High androgen level result in the formation of multiple small ovarian follicles.

In addition, androgens increase the number of FSH sensitivity in the ovaries, which results in increasing FSH sensitivity. High exogenous FSH or low estrogen production because of aromatase inhibitors will lead to growth of one or more ovarian follicles [(2)], Regarding previous studies and the result of the present study, we can assume that letrazole is a suitable alternatives to clomiphene citrate, especially in cases not responding to this drug, or it can be a first – line drug in ovarian stimulation and treatment of anovulation. It seems that letrazole and its drug group are safe reliable and cheap drug with therapeutic value [(7)]. On the other hand regarding the positive effect of letrazol in producing FSH sensitivity and satisfactory E2 elevation (as normal physiological levels), it can have better therapeutic effects in infertile females. In addition because serum clearance of letrazole is faster than clomiphene citrate (50 hr versus 4 weeks), and dose not lead to a decrease in the estrogen receptors it is probable that letrazole does not produce deleterious effect similar to that found with clomiphene citrate on the endometrium, although it can lead to pregnancy at similar or even higher rates[(7)]. However the optimum dose of letrazole remains unknown and further studies are necessary in the field [(11)]. The result of the current study compassing Metformin–clomiphene citrate with Metformin–letrazole in clomiphene resistant PCOS patients show that combined metformin–letrazole therapy leads to higher pregnancy rates with the maintenance of pregnancy until full term. In addition regarding that in the population under study, all the pcos patients were overweight (BMI 29–30 kg/cm^2) by complete chance, It seems that based on the findings of this studyand especially in these patients, compered Metformin– Letrazole is probably the best choice of therapy. although it has simple side effect such as hot flushes, breast tenderness and headache with no risk of multiple pregnancy and ovarian cyst or ovarian hyper stimulation.

Conclusion

Oral administrations of aromatase inhibitors (LETRAZOLE) are as effective as or superior to clomiphene citrate in ovulation induction and in super ovulation in an ovulatory infertility and for increased follicular recruitment. Unlike clomiphene citrate, they do not carry an estrogenic effect on endometerium so LETRAZOLE appears to avoid the unfavorable effects of antiestrogenic drugs on the endometerium.

Recommendation

1- We recommend to discuss the medical treatment for PCOS infertility with all patients before starting it (the cost, side effect & success rate).
2- Infertile PCOS with clomiphene–resistant should be better to be treated with metformin–letrazole for at least three menstrual cycles.
3- We suggest more wide population study and more number of ovulatory cycles to get better study results for the efficacy of letrazole as a new era of PCOS infertility treatment.

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