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COMPARISON BETWEEN THE EFFICACY OF COMBINED THE DRUGS: METFORMIN – LETRAZOLE WITH METFORMIN – CLOMIPHENE CITRATE IN POLYCYSTIC OVARIAN SYNDROME

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ABSTRACT

BackGround: The combination of the drug: Metformin and the antiestrogen (clomiphene citrate) in clomiphene –resistant PCOS patients enhance the ovulatory response of those patients. Although there is anti-estrogenic effects of clomiphene, it may be also associated with lower pregnancy rate. Inaddition to the the ovulation rate benefit, Letrazole is acting as an "aromatase inhibitor" which increases the ovulation rate without antiestogenic side effects of estrogen. **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:** Our research study is a "single – blind randomized clinical trial" ,one hundred mensturual cycles were studied in sixty patients with clomiphene – resistance having PCOS.They were selected among 115 patients with PCOS attending our infertility clinic in Samawa city – Iraq during the years 2011 – 2012. The Infertile female patients with PCOS were habhazardly divided into Metformin –Letrazole group who are 29 patients, and Metformin – clomiphene groups who are30 patients following an initial 6 – 8 weeks of gradual metformin use .The patients were received either the drug "Letrazole" (5mg) in two divided doses from2nd to 7th day or atiestrogen "clomiphene citrate" (100mg in two divided doses)daily from 5th to 9th day of menstrualcycle .The hormone "Estradiol" (E2) level , follicular numbers and the thickness of endometrium were examined on the day of HCG injection .The pregnancy rate of both groups also estimated. **Results :** The estimation of total E2 and E2& their mean for each mature follicle were found to be significantly elevated in clomiphene group, and there is no significant difference in mean number of mature ovarian follicles ≥ 18mm and their ovulation rate . There was significant increment of endometrial thickness with patient with Letrazole group . Thenumber of patients getting pregnancy in Letrazole group (10patients , 34.50%) as compared with clomiphene group (5 patients 16.6%),which did not reflect significant difference , while full – term pregnancies rate were more in Letrazole group (10patients 34.5%) in comparisim to 3patients (10%). **Conclusion :** In clomiphene resistant PCOS patients , the addition of Letrazole to Metformin causes higher full term pregnancies as compared with the use of clomiphene and Metformin.

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INTRODUCTION

Infertility has been attributed to many factors, amongst them the anovulation is the major causative factor in about 40% of all female infertilities. Polycystic ovarian syndrome (PCOS) is the commonest cause of "chronic anovulation" (Al-Fozan, 2004), the prevalence of which has been estimated to reach 6% in females with infertility (Rast, 2000). Polycystic ovarian syndrome (PCOS) "is one of the most common endocrine disorders in women of child bearing age". Although it is a commonest causative factor of female infertility due to chronic anovulation, its underlying cause still uncertain and its management is difficult. However, most presentations of PCOS can be effectively controlled or managed with adequate diagnosis and proper treatment. Therefore, treatment modalities and ovulation induction methods must be balanced for best results (Al-Fozan, 2004). Clomiphene citrate, is the first line drug for ovulation induction in patients with PCOS and can induce ovulation in 70 – 75% of patients .The best response is seen in 70% of patients as clomiphene citrate is administered in a dose of 50 – 100 mg / day. If the patients not respond to a dose of 150mg/ day with the endometrial

thickness under 6 mm in depth, they considered as clomiphene resistant (Al-Fozan, 2004). Some studies demonstrated that a high dose of antiestrogen "clomiphene citrate" has some side effects on female fertility and the early stages of fetal growth which is not proven in human studies (Ratukan, 2001). The studies has evaluated a significant difference between rates of ovulation and pregnancy and increasing miscarriage rates in patients taking clomiphene citrate therapy. So, the use of a simple safe oral drug , alternative to clomiphene citrate, can induce a new development in ovulation induction . Letrazole is "a newly prepared third generation selective aromatase inhibitor" which "acts by reversibly inhibiting the enzyme responsible for estrogen biosynthesis by reducing estrogen level in the body", Letrazole will enhance the hypothalamus and/ or pituitary gland from the "negative feedback of estrogen" in the pituitary gland which is causing increment in the level of endogenous "follicular Stimulating hormone" and "luteinizing hormone", which stimulates ovarian follicular development (Rast, 2000). With the above characteristics, which induce ovulation in infertile women with PCOS (Ratukan, 2001).

The pharmokinetics shows that half-life of Letrazol is about 2 days which means that it consumes about 48 hours for the drug concentration to decline in one – half in the patients serum. The drug will be completely excreated in 5 half lives. In the case of letrazoel, this is about 10 days. This it may be metabolized differently in younger women. The drug clearance is so slow and the volume distribution is approximately 2L/kg indicating that "it is widely distributed in the body"(2), (3) this increases the possibility that the drug or its metabolites could be adequately distributed to the ovary or uterus "organs vital for reproduction". The further studies has shown the effects of metformin in PCOS patients by increasing pregnancy rate and by reducing the complications of pregnancy such as gestational diabetes (Fisher, 2002). In addition, the beneficial effects of combined metformin – clomiphene therapy has also been reported in clomiphene – resistant PCOS patients (Flemina, 2002). Previous studies has also shown the beneficial effects of letrazole in clomiphene – resistant patients (Flemina, 2002), Although, no studies has yet compared the effects of complained metformin – letrazole treatment with patients of metformin – clomiphene citrate. The goal of this study was to compare and define the effect of addition of metformin – letrazole administration to that of metformin – clomiphene citrate in clomiphene citrate resistant patient in infertile woman with "PCOS".

MATERIALS AND METHODS

In our study single – blind randomized clinical trial,there was 120 ovarian cycles were studied in 60 patients who are clomiphene – resistant with PCOS features, who were selected among 115 PCOS patients coming to infertility clinic in Samawa city – Iraq during the years 2011 – 2012. The main features for diagnosis of PCOS were "oligo – and or anovulation, clinical or biochemical signs of hyperandorganism and polycystic ovaries" which are designed with the revised 2003 Rotterdam criteria of PCOS". The check up of thyroid functions, prolactin level, hysterosalp in geography and seminal fluid analysis were of normal values. Our study inclusion criteria were consisting of infertile PCOS patients not become pregnant after three courses of maximum dose of 150 mg of clomiphene citrate who are considered as clomiphene – resistant, whereas the above mentioned tests were normal.

Exclusion criteria: of our study including patients with history of hepatic and renal failure, cardiovascular disease , diabetes " based on criteria set by the American Diabetic Associations " or patients who consumed oral hypoglycemic agent "metformin" or any medications affecting insulin secretion and metabolism or ovulation induction drugs in the previous months. The patients were visiting the infertility clinic and examined by gynecologist and sonographists. A group of blind envelopes had numbers from 1 to 60 has been prepared . Each patients was asked to chose an envelope and was opened by the clinical secretory in either metformin – letrazole group "Group A" or Metformin – clomiphene citrates group "Group B". At first, all patients in the study of were received 1500mg Metformin "Glucophage" per day (500mg three times a day) for 6 - 8 weeks, started gradually. If pregnancy occurred, the patients was excluded from the study. In case of pregnancy failure after the end of the8 weeks period, the patients in the Metformin – clomiphene group (Group B) were given 100mg clomiphene citrate " clomid, sonafiaventi "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 cycles for 5 days.

The ovarian status was determined by transvaginal sonography on alternate days from day 12 of the cycle by a single sonagraphist "according to the length of previous cycles". A dose of 10000 Iu of pregnel vial "HCG" was injected to those in whose at least one ovarian follicle size $\geq$ 18 m in size. Estradiol (E2) level and the ratio of E2 to number of mature follicle were checked on the day of HCG injection. The patients were asked to have an intercourse every other day from 3 days prior to 5 days after ovulation "fertile window". Confirmation of ovulation and transvaginal sonography were performed. In case of delayed menstruation in a patient who had ovulated, beta – HCG was measured, and pregnancy was examined by transvaginal sonography. In pregnancy, f if fetal heart rate become positive, metformin was discontinued, and in case of therapeutic failure "negative beta-HCG", the patients was asked to continue with metformin and to return in their courses of treatment. The meeting of statisticians, sonogrophist and gynaecologist in this trial were blind to the type of therapy, while the patients were not blind to letrazole and clomiphene tablet, because of their known different shapes. S PSS version 22.0 software was involved for statistical analysis and the t – test and chi – square tests were used as necessary .If P – values less than 0.05 ,it were considered as "statistically significant".

RESULTS

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 the treatment with metformin for 6-8 weeks, one of the patients in the letrazole group became pregnant and was excluded from our study. A significant statistical difference was not present between group A and B taking in account mean demographic variables including age, BMI and duration of infertility and its type as shown in Table 1.

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

Mean total E2 and Mean E2 level per mature follicle on the day of HCG injection was significantly more within patients in the clomiphene group as compared with those patients in the group A (1664 ± 1349 and 981.35 ∓64844 pM/l in comparism to 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-).

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 %

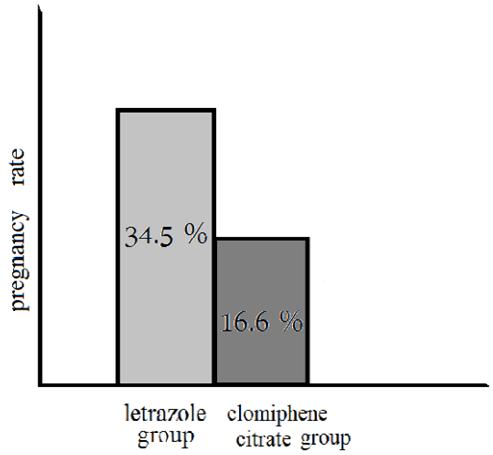

Figure 1. Pregnancy rate in letrazole Group and clomiphene citrate group in PCOS patient

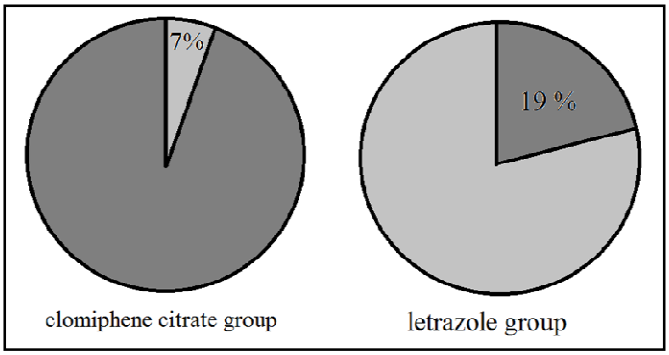

Figure 2. Pregnancy rate in each menstrual cycle for both clomiphene citrate group and letrazole groupe in PCOS patient

There are two abortions occurred in the clomiphene citrate group in the first 12 weeks of pregnancy, while there is no abortion was seen in the letrazole group. The gestational age in the time of delivery in both groups was between 37 and 39 weeks, with no preterm delivery. Mean fetal birth weight was 2860gm in group A and 2900gm in Group B, "which were both lighter than Iraq mean birth weight as it is 3100gm for girls and 3300gm for boys". There were no structural or congenital 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 getting pregnancy in each 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 (under table).

DISCUSSION

In our study, the results reflect that women with PCOS experience higher pregnancy rates and less abortions rate when they are taking combined metformin – Latrazolein compared 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 injection was significantly less in patients taking clomiphene citrate than those who received letrazole (0.55 ∓0.28 versus 0.22∓0.13 cm), which is similar to the result obtained by mitwally *et al* (2005). While, in the study acheived by Al – Fozan *et al* (2004), a significant relationship was not found between their two groups. It is may be the cause of endometrial thickening in patients taking letrazole is because of enhancement of vascularization as compared with clomiphene citrates (Fishes *et al*, 2002). Other studies also obsereved that clomiphene citrate can lead to improper 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 (Mitwaly and Casper, 2001). These complications may be due to the anti – estrogenic effects and the relatively longer half – life of clomiphene citrate, thus reducing endometrial thickness by its prolonged – term effects in declining the number of estrogen receptors (Mitwally and casper, 2001). A significant statistical relationship did not present between the reccurance of ovulation in either group; neither was there is a significant relationship between the mean number of mature ovarian follicles (diameter > 18mm).

In the study done by Al – Fozan *et al* (2004), a significant relationship did not obtained 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 acheived by mitwally *et al* (2005), the total number of mature follicles was significantly more in the letrazole group versus clomiphene citrate group. In the veiw 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 injection (1664.63 versus 981.38 pM/L and 783.38 versus 447.60 pM/1) High supra-physiological level of estrogen obtained during ovarian stimulation with clomiphene citrate may answer some of the side effects of clomiphene on the future of infertility treatment , although declining estrogen synthesis by aromatase inhibitor may reflect such adverse 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. Although, a significant relationship did not veiwed between the letrazole and clomiphene citrate groups in respect to pregnancy rate, There

is a non – significant increment in pregnancy rate was observed in patients who are taking 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. Due to two abortions happened 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 problem. The study performed by Mitwally and Casper (2001), which assessed the effect of letrazol treatment in 10 women with PCOS, showed that pregnancy occurred in a 20% of cases. Another study (Sammour *et al*, 2001), which also studied the effect of letrazole and clomiphene citrate in 49 women with unexplained infertility , also showed pregnancy rate to be higher in patients taking letrazole than those receiving clomiphene citrate (16.7 verus 5.6%). As shown in both studies, pregnancy rate is more in patients receiving letrazole than those taking clomiphene – citrate but is lower in comparism with the current study. Thus, we may conclude that the combination of Metformin – letrazol is better than letrazole alone, specially in overweight women who has more intense anovulatory status with higher androgen level producing more "resistant hypothalamic pituitary ovarian axis". Further studies are needed 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 obtained from the current study as well as previous ones , it shows 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 (Mitwally and caiper, 2002a). Hypotheses have been studied concerning the direct side effects of clomiphene citrate on oocytes, but views are variables .One of the causative factors of the low success rate of clomiphene citrate is improper uterine blood flow during the early luteal phase and the stage of implantation (Mitwally and casper, 2002a).

Finally, there are difficulties in ovulation in women with oligomenorrhea and PCOS, which may be because of insulin resistant and its related factors (Fleming *et al*, 2002). It is strongly believed that high serum insulin level is affected by PCOS pathogenesis. Metformin is an effective drug in diabetes and can enhance tissue sensitivity to insulin as well as reduce plasma insulin level and hepatic glucose production. In PCOS patients, metformin can reduce the level of LH – and ovarian androgen level as well as correct hyperinsulinanemia (Hecad *et al*, 2002). The effect of metformin on the activity of ovaries has been shown in clinical trials (Fleming *et al*, 2002) and has been shown to correct irregular menses by producing ovulation (Mitwally *et al*, 2005). In addition, Nestler *et al*, (1998) showed that metformin enhance ovarian response to clomiphene citrate in obese women with PCOS. According to this finding, the current study was normal in that who used metformin in combination with clomiphene and letrazole. Aromatase enzyme is necessary for converting and rostenodione to estrogen and finally to E2 in peripheral tissues (Bast *et al*, 2000). Aromatase inhibitors can prevent peripheral estrogen production in patients in whom peripheral estrogen secretion is increased (Bast *et al*, 2000). 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 letrazoleare used to induce ovulation especially in infertile women with PCOS (Mitwally and Casper , 2002a). The use of drug "aromatase inhibitors" in the initial follicular phase has a negative feedback effects on the hypothalamus and pituitary glands which is causing GnRH "LH and FSH" secretion with resultant ovarian follicular growth stimulation .They may also have direct effects on the ovaries and induce 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 induce the number of FSH receptor sensitivity in the ovaries, which results in increment in FSH sensitivity. High exogenous FSH or low estrogen production because of aromatase inhibitors will cause growth of one or more ovarian follicles (Bast *et al*, 2000), In respect to previous studies and the results of the present study, we can conclude that letrazole is a more suitable alternatives to clomiphene citrate, especially in cases not respond to this drug, or it can be a first – line drug in ovarian stimulation and treatment of anovulation. It is believed that letrazole and its drug group are safest drug which is reliable and cheap drug with therapeutic value (Mitwally *et al*, 2002).

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 does not cause a decrease in the estrogen receptors, it is probable that letrazole does not produce adverse effects similar to that found with clomiphene citrate on the endometrium , although it can lead to pregnancy at similar or even higher rates (Fisher *et al* , 2002). However the maximum dose of letrazole remains unknown and further studies are necessary in the field (Mitwally and casper 2005). The result of the new study using Metformin – clomiphene citrate with Metformin – letrazole in clomiphene resistant PCOS patients show that addition of 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 study and especially in these patients, compared 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 anovulatory 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

- We recommend to discuss the medical treatments for PCOS infertility with all patients before starting it (the cost, side effect & success rate).

- Infertile PCOS with clomiphene – resistant should be better to be treated with metformin – letrazole for at least three menstrualcycles.
- 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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