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Comparative effectiveness of pioglitazone, raloxifene, and combined pioglitazone-raloxifene of ovulation-induction therapies in infertile patients with resistant polycystic ovary syndrome

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ABSTRACT

Background: Clomiphene citrate (CC) has been the first line of treatment for ovulatory disorders for more than four decades, and clomiphene citrate alternative therapy is limited. This study aimed to compare the efficacy between (pioglitazone, raloxifene, and the combination of pioglitazone and raloxifene) for ovulation induction, and pregnancy in infertile women with resistance polycystic ovary.

Materials and methods: Eighty seven women suffering of polycystic ovary infertility have been assigned randomly to achieve ovulation induction with pioglitazone, 15 mg bid (GroupI), raloxifene, 60 mg bid for five days starting on the 3rd day of spontaneous or triggered menstruation, (Group II), or by the combination of pioglitazone, 15 mg twice daily and raloxifene 60 mg twice daily (GroupIII). Folliculometry was started from day 10 of the cycle and repeated every 2 days until day 16 of the cycle. HCG (5000-10000 IU) was administered I.M while at least one oocyte ≥ 18 mm was developed. To diagnose pregnancy, serum β-HCG was assessed 2 weeks after HCG injection.

Results: Variations in pregnancy rates among the three study groups were statistically important 20% (5/25), (30% (9/30), and 34.4% (11/32) for (pioglitazone, raloxifene, and the combination of the treatment groups, respectively) and the ovulation rates were, 44% (11/25), 73.3% (22/30), and 78.1% (25/32) for pioglitazone, raloxifene, and the combination of treatment groups, respectively).

Conclusion:

The use of raloxifene has shown more efficacy than pioglitazone, while the combination of (raloxifene and pioglitazone) has shown more efficacy than (raloxifene and pioglitazone) separated, as regards the ovulation and pregnancy rates in women that complain of infertility of primary or secondary origin with the resistance of polycystic ovary syndrome.

Keywords: ovulation induction, polycystic ovary syndrome, raloxifene, pioglitazone, infertility.

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INTRODUCTION

Ovulatory dysfunction is a common cause of reproductive failure in subfertile and infertile couples. Anovulation is the most prevalent form of ovulatory disorder and is called polycystic ovary syndrome, as the common cause of anovulatory infertility [1].

Clomiphene citrate (CC) is a standard first-line chronic anovulation treatment characterizing polycystic ovarian syndrome [2]. Clomiphene citrate rises up in the body through low clearance, prolonged $t_{1/2}$ (five days), and serum levels of active zu isomer CC are observable up to 42 days following treatment. Nevertheless, (20 to 25 percent) of polycystic ovarian syndrome (PCOS) women failure to ovulate with increasing CC doses [3]. There are a few options for those patients who do not respond to CC before starting on gonadotrophin medication or laparoscopic ovarian drilling. Due to the high sensitivity of gonadotropin in the ovaries to stimulate the women with PCOS, treatment with human menopausal gonadotropin (hMG) or pure FSH can induce numerous ovulatory oocytes, leading to multiple pregnancies and ovarian hyperstimulation syndrome [4]. The preferred treatment will therefore be a simple oral treatment that can be used without risk of ovarian hyperstimulation and reduced surveillance needs. Raloxifene is a selective estrogen receptor modulator (SERM) licensed to treat osteoporosis in post menopause women [5], with the hypothalamic and pituitary-like the antiestrogenic effects of tamoxifen and clomiphene citrate. Raloxifene can also have a beneficial effect on the indicators of endometrial receptivity relative to tamoxifen and clomiphene citrate [6], and FSH levels have improved in premenopausal women [7].

Insulin resistance is a major trait of PCOS and reduce glucose tolerance, type 2 DM, and gestational diabetes mellitus are commonly associated with this syndrome [8–10]. Insulin resistance is common among women with normal weight and overweight PCOS [11].

As a new class of insulin sensitizers, thiazolidinediones (TZDs) were introduced in 1998 and indicated responses close to the metformin use [12].The thiazolidinediones are peroxisome-proliferating receptor-activated agonists (PPAR), including pioglitazone, that lead to adipogenesis and have insulin-sensitization and antidiabetic properties [13].

The current study aimed to compare the efficacy of raloxifene, pioglitazone, and the combination between

raloxifene and pioglitazone in the induction of ovulation and achievement of pregnancy in PCOS women.

MATERIALS AND METHODS

This prospective randomized trial, approved by the local organizational ethicing and research board, was conducted in the infertility clinic of Al-Haj Jalal hospital in Waist, Iraq, from August 2019 to the end of May 2020, and it included 87 infertile women with PCOS who failed to ovulate when using clomiphene citrate at a dosage of 150 mg/day and expressed a desire for pregnancy. The diagnosis of PCOS was made according to Rotterdam's criteria [14].

Exclusion criteria included a history of diabetes or hepatic or thromboembolism disease and the use of any medication for at least 3 months before enrollment in this study, Cushing syndrome, thyroid dysfunction, hyperprolactinemia, and who were allergic to pioglitazone, or raloxifene was excluded. Women who met the inclusion and exclusion requirements of the study and decided to participate in the study were randomly assigned to obtain ovulation induction utilizing pioglitazone 15 mg twice daily at breakfast and dinner, (GroupI n=25), raloxifene 60 mg twice daily for five days starting on the 3rd day of spontaneous or triggered menstruation, (Group II n= 30) either separated or in combination with 15 mg twice daily pioglitazone (Group III n=32).

Transvaginal ultrasound (TVS) monitoring was performed on all patients on days 10- 16 of the cycle till mature follicles were detected. Therapeutic efficacy was considered when ovulation induction occurred (presence of follicles with a diameter of 16≥ mm on transvaginal ultrasound). Human chorionic gonadotropin (HCG) injection (Pregnyl 5000 –10000 IU I.M, Organon, Holland) was administered, when at least one follicle measuring ≥18mm was found. Patients were advised to have intercourse throughout 24–36 hrs. after injected HCG ampule. Patients were evaluated for ovulation signs (cul-de-sac fluid, disappearance of pre-ovulatory follicle, corpus luteum formation) two days after HCG was given. Serum HCG was determined 2 weeks after HCG injection for diagnosis of pregnancy in the absence of menstruation. A blood pregnancy test has been performed and pioglitazone stops after positive findings have been found in the pregnancy tests. The treatment plan had to be continued for women with a negative pregnancy test and those without ovulation. For three periods, the treatment protocol was followed for all groups. The safety profile consisted of blood samples analyzed for creatinine and liver function tests alanine transaminase (ALT) and aspartate transaminase (AST)

Statistical analysis

Continuous variable data is expressed as mean ± standard deviation (SD) and categorical variables as frequencies and percentages are presented. In the LSD test, the continuous variables were evaluated while categorical data were analysed using the Chi-Square test. The p-value ≤ 0.05 was deemed significant. All statistical analysis was conducted with version 9.1 of SAS (2012).

RESULTS

As described in table 1, there were no statistically significant variations in age, weight and duration of infertility between all groups. A statistically significant difference was found among all study groups for primary infertility and secondary infertility (P≤0.05).

Table 1: Baseline features in PCOS patients in all research groups.

Study variable	Pioglitazone Group I n=25	Raloxifene Group II n=30	Pioglitazone+Raloxifene Group III n=32	P-value
Age (years)	23.72±4.04	24.40±40	25.84±3.98	0.121NS
Weight (kg)	71.44± 13.67	68.79± 13.80	75.60±9.33	0.0952NS
Type of infertility Primary Secondary	17(68%) 8(32%)	22(73.3%) 8(26.7%)	23(71.9%) 9(28.1%)	0.0271*
Duration of infertility (years)[a]	5.08±3.37	4.30±2.55	6.15±3.47	0.0729NS

The effectiveness of all treatment groups was assessed concerning successful ovulation and pregnancy. The results are presented in Table 2, in the pioglitazone group the ovulation rate was 44% (11out of 25), 73.3% (22 out of 30), in the raloxifene group, and 78.1% (25 out of 32) raloxifene and pioglitazone combination group, and this is highly significant difference (p=0.0006). In compare with pioglitazone and raloxifene separated, the ovulation rate was higher with combination therapy after 3 cycles of follow-up.

In the pregnancy rate, there was a statistically significant difference (p=0.0263). In the pioglitazone group, five out of 25 (20 %) became pregnant, whereas nine out of 30 (30%) women in the raloxifene group got pregnant, and eleven out of 32(34.4%) in their combination group became pregnant (Table2).

Table 2: Effect of pioglitazone, raloxifene, and their combination on successful ovulation and pregnancy in PCOS patients.

Study variable	Pioglitazone Group I n=25	Raloxifene Group II n=30	Pioglitazone+Raloxifene Group III n=32	P-value
Ovulation rate	11(44%)	22(73.3%)	25(78.1%)	0.0006 **
Pregnancy rate	5(20%)	9(30%)	11(34.4%)	0.0263 *

Concerning the safety of pioglitazone, raloxifene and combination treatment groups, No elevation of liver enzymes was found (ALT and AST) <40.0U/L and serum creatinine <1 mg/dl were examined after three cycles of treatment in all groups. The mean value of serum ALT, AST, and creatinine was statistically non- significant (Table 3 and Table 4).

Table 3: Effect of pioglitazone, raloxifene, and their combination on Alanine transaminase (ALT) and aspartate transaminase (AST) in women with polycystic ovary

Study groups	Liver enzyme (U/L)			P-value
	Pre-treatment		Post-treatment	
Pioglitazone Group I n=25	**ALT**	20.35 ± 1.38	21.45± 1.34	0.217 NS
	AST	20.11± 1.18	20.99±1.12	0.873 NS
Raloxifene Group II n=30	**ALT**	19.55± 0.71	18.54± 1.35	0.561 NS
	AST	18.34 ±1.06	19.09± 0.56	0.603 NS
Pioglitazone+Raloxifene GroupIII n=32	**ALT**	18.88 ±0.66	19.19± 0.75	0.802 NS
	AST	19.87± 0.86	18.75±1.12	0.592 NS

Table 4: Effect of pioglitazone, raloxifene, and their combination on serum creatinine in women with polycystic ovary

Study groups	Serum creatinine level (mg/dl)		P-value
	Pre-treatment Mean ± SD	Post-treatment Mean ± SD	
Pioglitazone GroupI n=25	0.58 ± 0.13	0.62± 0.15	0.307 NS

Raloxifene GroupII n=30	0.66 ± 0.17	0.68 ± 0.12	0.569 NS
Pioglitazone+Raloxifene GroupIII n=32	0.71 ± 0.1	0.68± 0.08	0.327 NS

DISCUSSION

This first randomized study comparing pioglitazone, raloxifene and their combination for ovulation induction in women with PCOS resistance has shown a statistically significant ovulation difference among all study groups. On the basis of the study design, raloxifene and combination therapy in polycystic infertile women are superior to pioglitazone for ovulation induction.

Previous studies reported a controversial finding concerning the effect of pioglitazone treatment to improve outcomes in a variety of PCOS symptoms including ovulation induction and pregnancy rate. Pioglitazone has increased the ovulatory induction rate from 5.6 percent to 41.2 percent relative to placebo according to Brettenthaler *et al*. (2004). [15]. Thiazolidinediones therapy increases spontaneous pregnancy rate in many studies (20 to 40 percent success) [16]. Meanwhile, Sohrevardi *et al*. (2016) reported a pregnancy rate of (25%) after pioglitazone therapy for 3 months [17]. Consequently, clinical pregnancy occurred in 5/27 in the pioglitazone treated (18.5%) in obese insulin resistance (IR) women with PCOS [18]. In the present study where pioglitazone for three cycles in resistance PCOS patients produce (44%) positive ovulation and pregnancies (20%). Conversely, Hirotaka *et al* (2008) recorded that in an average of 11 weeks of initiation of pioglitazone, 7 from out 9 women (77.7 percent) succeeded in pregnancy and that 4 from out 7 pregnant women (57 percent) conceived in the first. [19], and Razzaq *et al* (2016) reported that the higher efficacy of pioglitazone group 82.86% than metformin group was 54.29% [20].

On the other hand, a previous study demonstrated the role of raloxifene in PCOS patients, Paula Guedes Neto *et al*. (2011) found that both clomiphene citrate and raloxifene induce ovulation of PCOS equally effective [21]. Dhaliwal *et al*. (2011) , found an ovulation rate at 40 mg and 80 mg doses using tamoxifen (60.6% and 63.6%, respectively), whereas pregnancy rate at dose of 80 mg (31.4%) higher than in dose of 40 mg (14.6%) per ovulatory cycle in women with clomiphene failure [22], Rashida *et al* (2012) showed that letrozole has ovulation rate (62.5%) in comparison to CC 37.5% and placebo in patients with CC- resistant PCOS[23].

In this study, raloxifene, and its combination with pioglitazone for three cycles in resistance PCOS patients produce (73.3% and 78.1%, respectively) positive ovulation and (30% and 34.4% respectively) pregnancy outcome. Raloxifene and its combination with pioglitazone display more successful ovulation success rate than pioglitazone. This result indicates that raloxifene is a successful ovulation inducer and is free of adverse effects and complications in women suffering from chronic anovulation. This may be attributed to the beneficial effects of raloxifene on the ovulation rate of endometrium. The PCOS endometrium of women appears to be dysfunctional [24]. The Estrogen receptor (ERα) is typically decreased in fertile women during the mid-secretory period [25], while the PCOS endometrium is highly expressible for this steroid receptor [26] and reduced expression of αvb3 expression [27], GRB2-associated binding protein 1and leukemia inhibitor factor [28]. These supposed endometrial defects and related progesterone resistance are further triggers for the use of anti-estrogen drugs, which may help the induction of ovulation in patients with polycystic ovarian syndrome. Besides the impact on levels of FSH, adequate antiestrogenic compounds can boost endometrial receptivity via preventing ERα behavior. In vitro research model, raloxifene seemed to have a beneficial effect on endometrial expression αvb3 [6], shorter $t_{1/2}$ of 32.5 hrs, and the absence of persistent systemic deposition in relation to clomiphene citrate (five-seven days)[29,30]. Raloxifene's shorter duration could remove the period of refractory found in clomiphene citrate therapy and risk of adverse effects on the embryo. Importantly, these data indicate that raloxifene has more efficacy to stimulate ovulation in PCOS resistance women.

Two twin pregnancy has occurred with the combination of pioglitazone and raloxifene, but all pregnancies with pioglitazone and raloxifene were singletons. Also, no adverse effects and ovarian hyperstimulation syndrome (OHSS) occurred with oral induction ovulation in all groups.

During the trial period, no major changes were mentioned as in the previous studies in liver enzymes and serum creatinine [31-33]. Extreme acute hepatic failure following troglitazone administration or heart failure following rosiglitazone administration were not detected after three cycles of pioglitazone administration

CONCLUSIONS

The use of raloxifene has shown more efficacy than pioglitazone, while the combination of (raloxifene and pioglitazone) has shown more efficacy than (raloxifene and pioglitazone) separated, as regards the ovulation and pregnancy rates in women that complain of primary or secondary infertility with the resistance of polycystic ovary syndrome.

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