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Comparative Study between Pioglitazone, Pioglitazone Plus Clomiphene Citrate and Metformine Plus Clomephine Citrate in Treatment of Polycystic Ovarian Syndrome

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ABSTRACT

Background: Polycystic ovarian syndrome (PCOS) is a prevalent metabolic & reproductive condition in females of reproductive age.

Aim and objectives: To assess the effectiveness of Pioglitazone, Pioglitazone plus Clomiphene citrate, Metformin plus Clomiphene citrate in treating infertility in PCOS.

Patients & methods: This was a randomized comparative study conducted on patients presented to the Outpatient Clinic of Gynecology of Om-Elmasrieen Hospital, complaining of infertility and diagnosed as having PCOS. Patients were divided into three groups.

Results: no significant variances in endometrial thickness, OHSS, and multiple pregnancies between three groups= 0.312, 0.360, 0.635 respectively. However, there were significant differences in drug-related complications, PRL before induction p=0.001, FSH, and Insulin levels p>0.05 before & after induction, but no significant differences in LH or Insulin levels p= 0.759, 0.377 respectively after 6 months.

Conclusion: pioglitazone is as effective as metformin without use of ovulation inducing drug. While metformin cannot be used alone. But it should combine with clomiphene citrate.pioglitazone can be used as an alternative to metformin as a single drug with the least side effects and complications and the same ovulation and pregnancy rates.

Key words: PCOS, Pioglitazone, Metformine, Clomephine Citrate

INTRODUCTION

PCOS is a prevalent metabolic and reproductive condition in women of reproductive age. Women with PCOS experience a set of symptoms related to monthly irregularities and excess androgens, which greatly affect their quality of life. There might be a higher occurrence of many health conditions, such as obesity, insulin resistance, type II diabetes mellitus, CVD, infertility, cancer, & psychiatric problems **(1)**.

Women with PCOS have anovulation because to a multifaceted interaction of many hormonal abnormalities. The hormones implicated include insulin, androgens, estrogen, progesterone, LH, FSH, adrenal androgens, TSH, prolactin, & other more. Women with PCOS are at an increased risk of developing insulin resistance, poor glucose tolerance, metabolic syndrome, obesity, & cardiovascular illnesses. Insulin

resistance is characterized by a diminished reaction to a certain quantity of insulin. Infertility is seen in 25-70% of patients with PCOS **(2)**.

Clomiphene citrate has been the primary treatment for stimulating ovulation in females with PCOS for many years **(3)**. The cost of the drug, the fewer side effects, and hence the good patient compliance, the need for less meticulous monitoring and little experience placed clomiphene citrate (cc) in that position. However, CC resistance develops in around 20%-25% of the patients **(4)**.

The American Society for Reproductive Medicine has reported that the use of new insulin sensitizers such biguanides & thiazolidinediones shows potential as a new therapy approach for PCOS, addressing both infertility & long-term disease prevention **(5)**.

The purpose of this research was to compare the efficacy of Pioglitazone, pioglitazone plus, clomiphene citrate, metformin plus & clomiphene citrate in the treatment of infertility in PCOS.

PATIENTS & METHODS

This was a randomized comparative study conducted on patients presented to the Outpatient Clinic of Gynecology of Om-Elmasrieen Hospital, complaining of infertility and diagnosed as having PCOS. Patients were separated into three groups: Group A: Pioglitazone. This drug used for 50 patients. Pioglitazone tablet (30 mg) given once per day for six months. Group B: Pioglitazone plus clomiphene citrate. Pioglitazone tablet (30mg) given once daily. Clomiphene citrate tablets (50 mg) given twice per day from the 2nd day of menstrual cycle for five days. Group C: Metformin plus clomiphene citrate. Metformin tablets (500mg) given twice daily and clomiphene citrate (50 mg) tablets from 2nd day of menstrual cycle for five days.

Sample size justification

A sample size of 45 patients per group was determined utilizing a power & sample size calculation algorithm version 3, based on a mean difference in Visual Analogue Scale (VAS) of 0.4 +/- 0.5 **(6)**. power of research=80 percent & alpha error =0.05.

Inclusion criteria: Infertile female either primary or secondary infertility

Normal semen analysis of the husband, normal hystero-salpingography and no congenital anomalies of the female genital system.

Exclusion criteria: Abnormal semen analysis of the husband, abnormal hysterosalpingography and other causes of infertility as intrauterine synechia or abnormal post-coital test.

Allocation and Concealment

Women were categorized into three categories based on a series of random numbers produced by a computer. The assignment was completed using opaque, sealed envelopes that are easy to open. The envelope is opened when an individual arrives at the clinic.

Methods

All patients were subjected to the following: A detailed history taking: personal history, obstetric history, menstrual history, past history and family history, Physical examination: General, abdominal, pelvic examinations were done to detect PCO patients fit for the study, Laboratory investigations: Semen analysis for the husband, FSH, LH, PRL at the 2nd day of the menses, Fasting and postprandial blood insulin. Hormonal profile and folliculometry were done to evaluate the efficacy of each drug used. Follow-up of ovulation was done using vaginal ultrasound for 6months.

Ultrasound study

The study assessed endometrial thickness and leading follicle size during menstruation, using serum and plasma samples from early follicular phases. Patients were randomized to receive pioglitazone, metformin with clomiphene citrate, or pioglitazone with clomiphene citrate. Folliculometry was performed daily until a dominant follicle ≥18mm in diameter was reached. Ovulation was confirmed by serum progesterone. If ovulation was found, the insulin sensitizer was discontinued. If no ovulation was found, the treatment continued.

Outcome measurements

Primary outcome: Endometrial thickness, dose of drug used and Follicular size monthly**. Secondary outcome:** Pregnancy **rate,** abortion rate, Gestational DM**. Complications:** Ovarian Hyper-stimulation Syndrome, Multiple pregnancies and Side effects of drug used.

Statistical analysis

IBM SPSS statistics (V. 25.0, IBM Corp, USA, 2016) was utilized for data analysis. Date was expressed as Mean ±SD for quantitative parametric measures in addition to number & percentage for categorized data. The following tests were performed: Analysis of Variance (ANOVA), Chi-square test and Calculated Relative Risk Assessments.

RESULTS

Table (1): Demographic data for the three groups

	Pioglitazone group (n=50)	**Pioglitazone & Clomiphene citrate group (n=50)**	**Metformin & Clomiphene citrate group (n=50)**	**F**	**P value**	
Age (Years)						
- Mean ± SD	31.48±4.263	30.2±4.305	30.04±3.923	1.794	0.17	NS
- Range	23 – 39	20 – 37	21 – 37			
BMI (kg/m^2)						
- Mean ± SD	27.5±2.61	28.1±2.54	27.7±5.62	2.353	0.15	NS
- Range	24 –31	24.2 – 30.5	23.8 – 31.1			

Data presented as range, mean ± SD; or number (percentage), BMI = body mass index, P > 0.05 = not significant, P < 0.05 = highly significant, SD= standard deviation NS= non-significant

no significant variance was noted between three groups as age and BMI p= 0.17, 0.15 respectively. (Table 1)

Table (1): Parity of the three groups

			Groups			**Total**
			Metformin & Clomiphene citrate	**Pioglitazone**	**Pioglitazone & Clomiphene citrate**	
Parity	**Multi**	**Count**	22	25	20	67

		%	44.0%	50.0%	40.0%	44.7%
	Nulli	Count	28	25	30	83
		%	56.0%	50.0%	60.0%	55.3%
Total		Count	50	50	50	150
		%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests		
	Value	P
Pearson Chi-Square	1.025[a]	0.599

No significant variance was noted among three groups concerning parity p=0.599. (Table 2)

Table (3): Endometrial thickness among the three groups

	Pioglitazone group (n=50)	Pioglitazone & Clomiphene citrate group (n=50)	Metformin & Clomiphene citrate group (n=50)	F	P value	
Endometrial thickness				1.794	0.312	NS
- Mean ± SD	9.72±1.41	10.12±2.23	9.8±1.67			
- Range	23 – 39	20 – 37	21 – 37			

No significant variance among three groups concerning Endometrial thickness p= 0.312. (Table 3)

Table (4): Difference between groups regarding OHSS

			Groups			Total
			Metformin & Clomiphene citrate	Pioglitazone	Pioglitazone & Clomiphene citrate	
OHSS	Negative	Count	48	50	49	147
		%	96.0%	100.0%	98.0%	98.0%
	Positive	Count	2	0	1	3
		%	4.0%	0.0%	2.0%	2.0%
Total		Count	50	50	50	150
		%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests		
	Value	**P**
Pearson Chi-Square	2.041[a]	0.360

No significant variance among three groups concerning OHSS p=0.360. (Table 4)

Table (5): Difference between groups regarding multiple pregnancies

			Groups			Total
			Metformin & Clomiphene citrate	Pioglitazone	Pioglitazone & Clomiphene citrate	
Multiple. Preg	Negative	Count	47	49	47	143
		%	94.0%	98.0%	94.0%	95.3%
	Positive	Count	1	0	2	3
		%	2.0%	0.0%	4.0%	2.0%
	Twin pregnancy	Count	2	1	1	4
		%	4.0%	2.0%	2.0%	2.7%
Total		Count	50	50	50	150
		%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests		
	Value	**P**
Pearson Chi-Square	2.556[a]	0.635

No significant variance among three groups concerning multiple pregnancies p=0.635 (Table 5)

Table (6): Difference between groups regarding complications of drug used

			Groups			Total
			Metformin & Clomiphene citrate	Pioglitazone	Pioglitazone & Clomiphene citrate	
Comp. drug. Used	No	Count	4	40	31	75
		%	8.0%	80.0%	62.0%	50.0%
	Yes	Count	46	10	19	75
		%	92.0%	20.0%	38.0%	50.0%
Total		Count	50	50	50	150

	%	100.0%	100.0%	100.0%	100.0%

Chi-Square Tests		
	Value	**P**
Pearson Chi-Square	56.160[a]	0.000

A highly statistically significant variance among three groups regarding complications of drug used p=0.0001. (Table 6)

Table (7): Hormonal profile of the three groups before induction

	Pioglitazone group (n=50)	**Pioglitazone & Clomiphene citrate group (n=50)**	**Metformin & Clomiphene citrate group (n=50)**	**F**	**P value**	
FSH (IU/L) **Mean ± SD** **Range**	4.692±1.84831 1.8 – 8.6	5.554±1.78614 2.2 – 9.1	5.3898±1.76151 2.4 – 8.4	3.236	0.042	S
LH (IU/L) **Mean ± SD** **Range**	9.826±2.21649 4.8 – 13.4	10.7318±1.96605 6.3 – 13.9	10.725±2.36175 5.2 –14.4	2.916	0.057	NS
PRL (ng/mL) **Mean ± SD** **Range**	15.6±4.23604 5.6 – 22	13.1076±5.71992 1.9 – 22	16.6022±3.3682 9.2 – 21.9	7.471	0.001	HS
Insulin (uIU/mL) **Mean ± SD** **Range**	36.388±4.05733 29 – 45.7	34.0624±3.63574 27.9 – 42.9	35.1284±4.97185 4.5 – 40.9	3.737	0.026	S

A highly statistically significant variance among three groups **before induction** concerning PRL p=0.001, as well as a statistically significant variance as regards FSH and Insulin p=0.042, 0.026 correspondingly, but no significant variance as regards LH p= 0.057 was noted. (Table 7)

Table (8): Hormonal profile of the three groups after 6 months

	Pioglitazone group (n=50)	**Pioglitazone & Clomiphene**	**Metformin & Clomiphene**	**F**	**P value**	

		citrate group (n=50)	**citrate group (n=50)**			
FSH (IU/L) **Mean ± SD** **Range**	4.892±1.9481 1.7 – 8.6	5.324±1.6814 2.4 – 8.3	5.478±1.652 2.3 – 8.6	3.316	0.042	S
LH (IU/L) **Mean ± SD** **Range**	6.5784±2.19022 2.7 – 11.4	6.9048±2.29626 2.9 – 11.2	6.7512±2.09328 2.4 – 11.7	0.277	0.759	NS
PRL (ng/mL) **Mean ± SD** **Range**	15.3±4.3704 5.9 – 21	13.286±5.5187 1.8 – 23	16.6022±3.3682 8.6 – 22	7.471	0.001	HS
Insulin (mIU/L) **Mean ± SD** **Range**	30.614±5.18329 22.3 – 45.7	29.4792±4.03417 22.4 –37.7	30.5122±4.12776 24.2 – 38.9	0.983	0.377	NS

A highly statistically significant variance among three groups concerning PRL= 0.001, as well as a statistically significant variance among three groups after 6 months as regards FSH p=0.042, but no significant variance as regards LH & Insulin p= 0.759, 0.377 respectively. (Table 8)

DISCUSSION

Polycystic Ovarian Syndrome impacts five to twenty percent of women in their reproductive years globally. PCOS is defined by hyperandrogenism, ovulatory dysfunction, & polycystic ovarian morphology (PCOM), with the ovaries producing excessive androgens being a crucial aspect of the illness. The majority of afflicted people have metabolic dysfunction, which is defined by insulin resistance & compensatory hyperinsulinemia **(7)**.

Thiazolidinediones had a notably lesser impact on BMI compared to metformin. Thiazolidinediones (TZDs) were equally effective as metformin in improving insulin sensitivity and reducing androgen levels in patients with PCOS, although they were less successful in promoting weight reduction **(8)**.

Metformin's present usefulness in treating ovulatory infertility in PCOS is restricted. Metformin is not indicated as the first treatment for inducing ovulation in women with PCOS who are not ovulating. It may be considered as a secondary treatment option in combination with clomiphene citrate for women with PCOS who are resistant to clomiphene citrate or are obese **(9)**.

Pioglitazone can impact reproductive hormones in PCOS by acting directly on the ovary or indirectly by lowering insulin levels in the bloodstream **(10)**.

The age of women was not statistically significant while the Body mass index was significant.

Ortega-Gonazalez et al.,. conducted a study comparing the outcomes of treating women with PCOS with metformin and pioglitazone for a duration of six months. This research found no significant variance among both groups in terms of insulin sensitivity, hyperandrogenism, menstrual cycle patterns, & successful pregnancy rates.

Weight changes, as increased BMI & waist-hip ratio, were greater in individuals who received pioglitazone compared to those who received metformin**(11)**.

Karoon-Shahebrahimi et al., found that Pioglitazone leads to a notable improvement in endocrine & metabolic markers. Pioglitazone can serve as a substitute medication for those unable to tolerate metformin **(12).**

Brettenthaler et al. shown that pioglitazone can alleviate insulin resistance, hyperandrogenism, & ovulation & menstrual cycle irregularities in women with PCOS**.**

Brettenthaler et al. & Rautio et al. documented same findings in obese women with PCOS **(13,14)**.

Ghazeeri et al., detected that Metformin & other insulin-sensitizing medications decrease insulin resistance and hyperinsulinemia, leading to a reduction in ovarian and adrenal hyperandrogenism. This often restores normal production of LH and FSH, promoting regular ovulation cycles & increasing the likelihood of conception **(15)**.

The outcomes of the present investigation align with findings from previous investigations on these medicines.

Ote et al., studied the efficiency of pioglitazone monotherapy on fecundity in nine infertile cases with PCOS who were resistant to clomiphene and dexamethasone. The dose of pioglitazone ranged from15-30 mg/day and the treatment continued for up to 32 weeks. Seven out of nine women conceived after an average of 11.3 weeks of starting treatment. The reported pregnancy rate was impressively high (77.78%) **(16)**.

The discrepancy in outcomes may be attributed to the initial usage of low dosages of pioglitazone in our trial. The low pregnancy rate in the pioglitazone group can be attributed to the increased likelihood of ovulation & pregnancy with larger doses of pioglitazone.

Glueck et al. administered metformin to 19 out of 22 individuals with PCOS & maintained the treatment throughout pregnancy. Consequently, they found that the miscarriage rate was ten percent **(17).**

Glueck et al. reported in an updated report that the incidence of miscarriage among 72 percent of pregnant subjects substantially decreased from 62 percent prior to treatment to 17 percent following the administration of metformin to seventy-two subjects with PCOS **(18)**.

These results are matching with our results which detected decreased rate of miscarriage with metformin 6% while with pioglitazone was 10%.

Initial findings by **Richard et al**. indicate that insulin-sensitizing pharmaceuticals might exert advantageous impacts on the endometrium. Furthermore, the authors propose that rosiglitazone might offer greater therapeutic benefits in comparison to metformin **(19)**. This result is matching with our study

Finally, According to **Ziaee et al.,** pioglitazone is safer than metformin in terms of side effects. This finding is corroborated by a randomized clinical trial that compared the two medications' ability to improve insulin resistance & cardiovascular risk factors in 52 women with PCOS between the ages of twenty & forty-five**(20)**.

CONCLUSION

pioglitazone is as effective as metformin without use of ovulation inducing drug. While metformin cannot be used alone. But it should combine with clomiphene citrate.pioglitazone can be used as an alternative to metformin as a single drug with the least side effects and complications and the same ovulation and pregnancy rates.

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