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Pharmacy department 10th batch

Research title Evaluation the Effect of Metformin on the treatment of Polycystic Ovary Syndrome (PCOS) by comparison with the effect of clomiphene citrate in Iraq.

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Abstract

Objective: To evaluate the difference between using metformin as a monotherapy to treating PCOS and the combination of metformin plus clomiphene within Holy Karbala, Babylon and Basra provinces, Iraq

Methods: In this single-blind randomized study, one hundred sixty females with PCOS, aged 12 - 60 years, up to eighty of them treated with metformin only therapy, whereas eighty of them treated with combination of metformin plus clomiphene. Comparison between two groups were depend on the changes of biochemical tests (LH: FSH-ratio, total testosterone levels and IR) and appearance of ovary ultra sound (ovarian size and morphology), of both groups to treat or minimizing the risk of PCOS. The data were analyzed by statistical software SPSS (version 27.0) and the significance of difference between mean values were estimated by paired sample T-test. $P < 0.05$ was considered statistically significant.

Results: In both groups there were highly significant differences between pre and post treatments regarding the insulin resistance. For LH: FSH-Ratio and total testosterone parameters, there were highly significant differences between pre and post treatment results for patients who had combination treatments, but no significant differences in patients who had metformin treatment alone. Finally, the ovary size in both groups were significantly differences between pre and post treatment.

Discussion: Our data show that BMI in both groups were lowered after course of treatment regimen, which confirm that metformin had role in modification of body weight in PCOS patients, at the same time the improvement in insulin resistance were done in both groups, Regarding ovary size, our data show that the metformin had beneficial effect on the ovary size, but the combination therapy had more positive effect on the ovary size due to the role of clomiphene citrate in improvement of ovary state.

Conclusion: The using of combination therapy of clomiphene citrate plus metformin pointed out the preference over using metformin alone for hyperandrogenism state in PCOS patients.

Introduction:

Polycystic ovary syndrome (PCOS) remains a key public health burden as it is one of the most common endocrine and metabolic disorders affecting 8%–13% of women globally.¹ The 2003 Rotterdam diagnostic criteria for adult women were updated and internationally endorsed in the 2018 International PCOS guideline.² Two of three clinical features are required in adults: (1) ovulatory and menstrual dysfunction, (2) biochemical and/or clinical hyperandrogenism, and (3) polycystic ovary morphology on ultra-sound, and accompanying insulin resistance (IR) with associated compensatory hyperinsulinemia.¹

Anovulation cycles might have a decreased fertility, and result in dysfunctional uterine bleeding, in addition to cutaneous manifestations of hyperandrogenemia in the PCOS such as acne, male-pattern hair loss (androgenic alopecia), hirsutism, and Acanthosis nigricans which is considered as a hyperinsulinemia cutaneous marker.³ Metabolic Complications include the Insulin Resistance and Type 2 Diabetes: Women with PCOS often exhibit insulin resistance, increasing their susceptibility to type 2 diabetes. Obesity and Metabolic Syndrome: PCOS is linked to a higher prevalence of obesity and metabolic syndrome, a cluster of conditions that elevate the risk of cardiovascular diseases.⁴

Evidence suggests that women with PCOS have an increased risk of heart disease and other cardiovascular conditions, elevated blood pressure is more common among women with PCOS, further contributing to cardiovascular risk.⁴

Approximately 85%–90% of women with oligomenorrhea (infrequent menstrual periods) and 30%–40% with amenorrhea (absence of menstrual periods) is diagnosed with PCOS.⁵

Lifestyle Modifications and dietary Interventions should be considered, adopting a low glycemic index (LGI) diet has been shown to effectively alleviate insulin resistance in women with PCOS. Professional dietary counseling is recommended to facilitate sustainable dietary changes. Physical Activity and regular exercise is advocated to improve metabolic parameters and support weight management. Combining aerobic and resistance training yields beneficial outcomes.⁶

Combined Hormonal Contraceptives (CHCs) primarily used to regulate menstrual cycles and alleviate hyperandrogenic symptoms such as hirsutism and acne. They function by suppressing ovarian androgen production and increasing sex hormone-

binding globulin, thereby reducing free testosterone levels. While effective, CHCs may not be suitable for individuals with certain contraindications, such as a history of thromboembolic disorders. It's essential to evaluate each patient's risk factors before initiation. ⁷

Metformin traditionally used for type 2 diabetes, addresses insulin resistance in PCOS patients, aiding in the restoration of regular ovulatory cycles. Metformin enhances insulin sensitivity, leading to decreased insulin levels and, subsequently, reduced ovarian androgen production. It must be considered that the common side effects include gastrointestinal disturbances. Gradual dose escalation can help mitigate these effects. Metformin is particularly beneficial for patients with impaired glucose tolerance. ⁸

Anti-Androgen agents target symptoms of androgen excess, such as hirsutism, acne, and alopecia. Spironolactone: An aldosterone antagonist can also block androgen receptors, reducing hair growth and acne, with regular monitoring of electrolyte levels is recommended. ⁹

Ovulation Induction Agents seeking to conceive, these agents stimulate ovulation (clomiphene Citrate) a selective estrogen receptor modulator that induces ovulation. Monitoring for ovarian hyperstimulation and multiple pregnancies is essential during treatment. ¹⁰

Aim of the study:

1. To evaluate the prevalence of PCOS in Iraq, particularly in Karbala, Hila and Basra provinces.
2. To examine the role of metformin in the treatment of PCOS.
3. To compare the effect of combination therapy of (metformin and clomiphene) with metformin alone in the coarse regimen of PCOS patients.

MATERIALS AND METHODS:

This study was conducted at the Gynecology outpatient clinics, AL-Hussain Teaching Hospital, / Karbala, Aleskandria public Hospital/ Babylon and Ibn-GHazwan teaching Hospital/ Basra provinces/ Iraq. Subjects were randomly selected from the patients attending the hospitals (80 Karbala ,60 Babylon and 20 Basra) during the period from September 2024 to February 2025.

The study included two groups: PCOS treated with metformin and the PCOS treated with metformin plus clomiphene. A total number of 160 study subjects were chosen to participate in this study with different age ranged between (12-55) years female sex was classified into two categories. Combination treatment (n=80). Metformin as a monotherapy (n=80).

Exclusion criteria:

- 1- Postmenopausal women.
- 2- Patients with severe or uncontrolled DM.
- 3- Patients with history of lactic acidosis.
- 4- Pregnant women.
- 5- Patients who suffer from severe renal or liver impairment.
- 6- Patients with endocrinal disorders or other hormonal disorders.

Statistical analysis:

Statistical analysis was done by SPSS statistical software (SPSS 27.0 for Windows, standard version). Descriptive analysis was used to show the mean and standard deviation of variables. Continuous variables were tested for normality according to the Kolmogorov-Smirnov test. The significance of difference between mean values were

estimated by paired sample T-test. The probability $P < 0.05$ = significant, $P > 0.05$ = non-significant.

Results:

One hundred sixty poly-cystic ovary syndrome (PCOS) patients [80 women were treated with combination (metformin + clomiphene) therapy classified as group A and 80 women were treated with metformin therapy alone classified as group B] enrolled in this study. The Baseline (pre-treatment) clinical, hormonal and metabolic characteristics for study participants were carried out statistically by using the paired sample T-test analysis, as summarized in Table-1.

	parameters	Group A (No = 80) (Mean $\pm$ SD)	Group B (No = 80) (Mean $\pm$ SD)	P- value
1	Age	27.9 $\pm$ 6.7	27.5 $\pm$ 6.4	NS
2	BMI	32.2 $\pm$ 4.3	32.7 $\pm$ 4.1	NS
3	Ovary size	12.45 $\pm$ 1.4	12.35 $\pm$ 1.4	NS
4	LH: FSH - Ratio	2.78 $\pm$ 0.4	2.78 $\pm$ 0.4	NS
5	Total Testosterone	63.70 $\pm$ 7.2	64.77 $\pm$ 7.8	NS
6	IR	4.45 $\pm$ 0.8	4.37 $\pm$ 0.8	NS

TABLE1 Baseline (pre-treatment) clinical, hormonal, and metabolic characteristics of PCOS patients.

(SD= standard deviation, BMI= body mass index, LH= luteinizing hormone, FSH= follicular stimulating hormone, IR= insulin resistance, NS= non-significant)

According to the baseline (pre-treatment) characteristic results presented in table-1, the (Mean $\pm$ S.D) of age of two study groups showed no significant differences ($P > 0.05$). Body Mass Index (BMI) of two study groups showed no significant differences ($P > 0.05$). Ovary size of two study groups showed no significant differences ($P > 0.05$). Also, the (Mean $\pm$ S.D) of LH: FSH-Ratio of two study groups showed no significant differences ($P > 0.05$). As well as, the Total Testosterone level of two study groups

showed no significant differences ($P > 0.05$). Finally, the insulin resistance (IR) of two study groups showed no significant differences ($P > 0.05$).

TABLE 2 comparison between pre and post treatment factors of response for Combination (metformin with clomiphene) and metformin.

factors	Group A Combination			Group B Metformin		
	Pre-treatment (Mean $\pm$ SD)	Post-treatment (Mean $\pm$ SD)	P-value	Pre-treatment (Mean $\pm$ SD)	Post-treatment (Mean $\pm$ SD)	P-value
BMI	32.2 $\pm$ 4.3	30.2 $\pm$ 4.4	< 0.05*	32.7 $\pm$ 4.1	30.6 $\pm$ 4.7	< 0.05*
IR	4.45 $\pm$ 0.8	1.92 $\pm$ 0.5	< 0.01**	4.37 $\pm$ 0.8	2.07 $\pm$ 0.6	< 0.01**
Ovary Size	12.45 $\pm$ 1.4	7.35 $\pm$ 1.3	< 0.01**	12.35 $\pm$ 1.4	9.54 $\pm$ 1.6	< 0.05*
LH: FSH	2.78 $\pm$ 0.4	1.55 $\pm$ 0.3	< 0.01**	2.78 $\pm$ 0.4	2.46 $\pm$ 0.4	NS
Total Testosterone	63.70 $\pm$ 7.2	35.93 $\pm$ 6.7	< 0.01**	64.77 $\pm$ 7.8	55.89 $\pm$ 9.3	NS

(SD= standard deviation, LH= luteinizing hormone, FSH= follicular stimulating hormone, IR= insulin resistance, NS= non-significant,)(* Significant at $P < 0.05$, ** highly significant at $P < 0.01$)

According to data on Table-2, which involve the comparison between pre and post treatment factors of responses of two groups were analyzed by paired sample T-test. For group A, which represent combination therapy (clomiphene plus metformin), BMI showed significant differences ($p < 0.05$) between pre and post treatment, IR showed highly significant differences ($p < 0.001$) between pre and post treatment, ovary size also showed highly significant differences ($p < 0.001$) between pre and post treatment. Furthermore, LH: FSH-Ratio showed highly significant differences ($p < 0.001$) between pre and post treatment. Finally, total testosterone level showed highly significant differences ($p < 0.001$) between pre and post treatment.

In contrast, for group B, which represent the metformin therapy alone, BMI showed significant differences ($p < 0.05$) between pre and post treatment and IR showed highly significant differences ($p < 0.001$) between pre and post treatment, also, ovary size showed significant differences ($p < 0.05$) between pre and post treatment. whereas, LH: FSH-Ratio showed no significant differences ($P > 0.05$) between pre and post treatment. Finally, total testosterone level showed no significant differences ($P > 0.05$) between pre and post treatment.

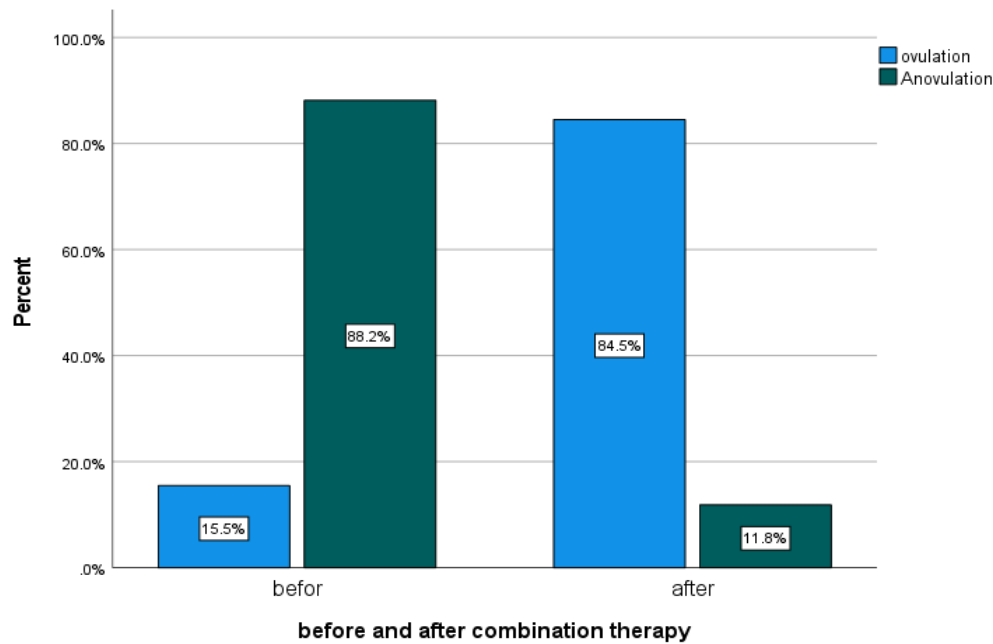


Figure-1: the ovulation state for group A patients between before and after treatment.

According to data on Figure-1, for group A (combination therapy) which illustrate the ovulation state between before and after treatment, only 15.5% of patients were ovulated before treatment versus 84.5% of patients ovulated after treatment.

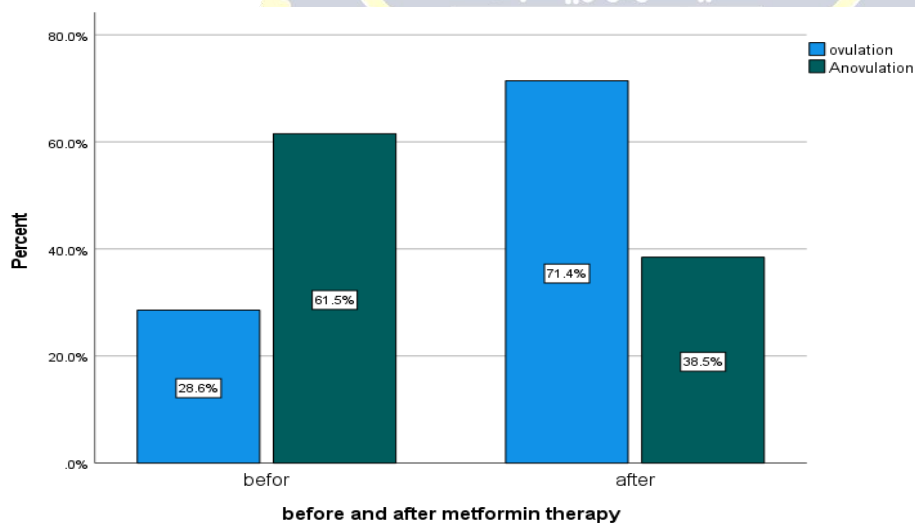


Figure-2: the ovulation state for group B patients between before and after treatment.

According to data on Figure-2, for group B (metformin therapy) which illustrate the ovulation state between before and after treatment, it was found that only 28.6% of patients were ovulated before treatment versus 71.4% of patients ovulated after treatment.

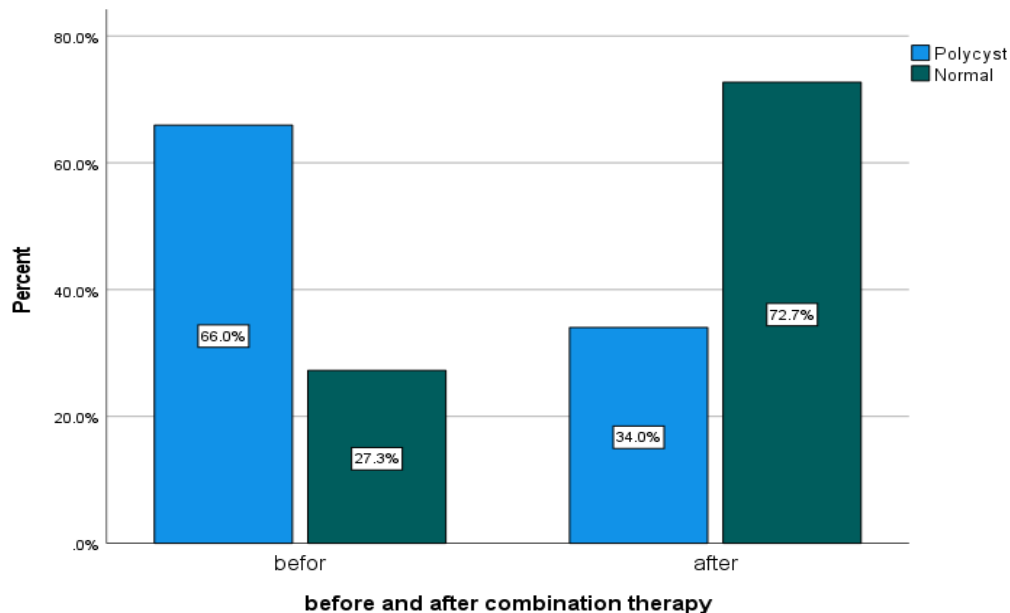


Figure-3: the ovary morphology for group A patients between before and after treatment

According to data on Figure-3, for group A (combination therapy) which illustrate the ovary morphology for patients before and after treatment, only 27.3% of patients had normal morphology before treatment versus 72.7% of patients had normal morphology after treatment.

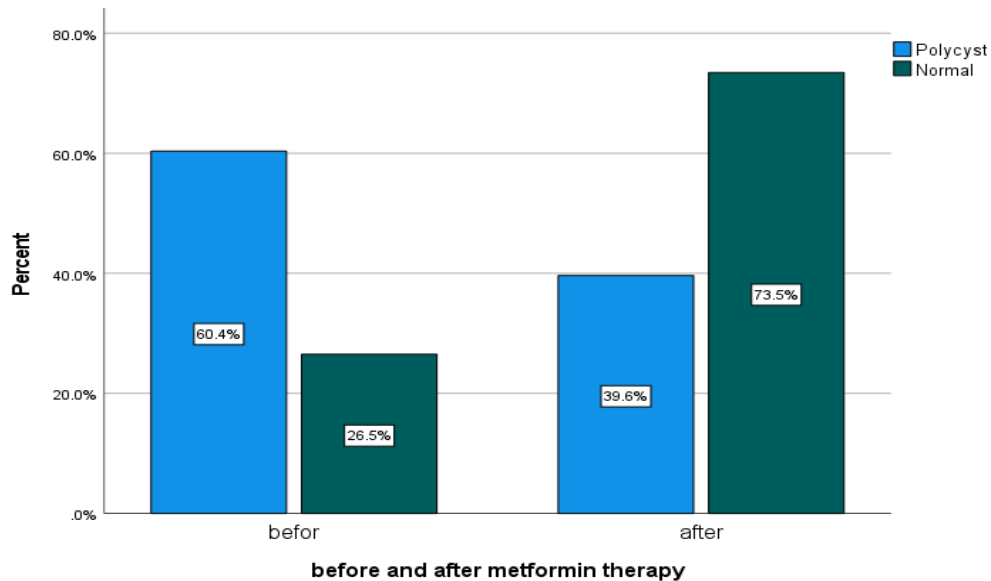


Figure-4: the ovary morphology for group B patients between before and after treatment

According to data on Figure-4, for group B (metformin therapy) which illustrate the ovary morphology for patients before and after treatment, only 26.5% of patients had normal morphology before treatment versus 73.5% of patients had normal morphology after treatment.

Discussion:

Many studies had been conducted on different types of medicines used in PCOS treatment, most studies have demonstrated the efficacy of metformin in inducing ovulation ⁽¹¹⁾, whereas other reports dispute this finding ⁽¹²⁾. Our study directly compares metformin alone to combination (metformin and clomiphene) the standard of treatment for infertility in the PCOS patient. More importantly, our study has the benefit of having 160 patients with an average follow-up of about 3 months.

Our data show that BMI in both groups were lowered after course of treatment regimen, which confirm that metformin had role in modification of body weight in PCOS patients, at the same time the improvement in insulin resistance were done in both groups. The decision for choosing the metformin medication was based on multiple factors. Because metformin has been shown to decrease weight and improve the metabolic profile, the more obese patients were more likely to choose

this treatment initially. All of this explains why parameters for metabolic syndrome were more common in the groups taking metformin.

Regarding ovary size, our data show that the metformin had beneficial effect on the ovary size, but the combination therapy had more positive effect on the ovary size due to the role of clomiphene citrate in improvement of ovary state. A similar result was noted in a study by Palomba et al ⁽³⁾.

With respect of hormonal results, our study demonstrates that the LH: FSH-Ratio had highly change during the course of treatment with combination therapy when compared with no significant effect of metformin on this parameter, these indicate the role of clomiphene citrate in the rearrangement of hormonal disruption that occur in PCOS patients. At the same time the total testosterone level was seduced significantly with using the combination regimen, whereas, metformin alone had no significant effect on the total testosterone level during the course of treatment.

In our study, the ovulation rate obtained with both medications was similar, so there was no additional benefit to the combination for ovulation induction compared with taking metformin alone. This result agreed with previous study which state "Metformin is better than clomiphene citrate for ovulation induction and equivalent for pregnancy achievement." ⁽¹³⁾

Conclusion and Recommendation:

our study shows that metformin is better for correction of body weight, improvement of insulin resistance and enhancement of ovulation rate than clomiphene citrate alone for PCOS patients. But the using of combination therapy of clomiphene citrate plus metformin pointed out the preference over using metformin alone for hyperandrogenism state in PCOS patients. Considering the efficacy of metformin, its better safety profile, its low cost, and its known beneficial effects on the overall metabolic profile, it is a very attractive therapeutic modality. Therefore, we propose that combination of (clomiphene plus metformin) can be offered as first-line therapy in all anovulatory patients with PCOS.

Because our research period is short, we recommend conducting similar research to continue following up on patients until they reach pregnancy and birth time.

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