Al-Azhar International Medical Journal

Volume 5 | Issue 1 Article 37

2024
Section: Obstetrics and Gynecology

A randomized, controlled trial comparing the metformin, oral contraceptive pills and their combination in patients with polycystic ovarian syndrome

Hamed Mohamed Hamed Abd El Rahman
MBBCh of Obstetrics and Gynecology, Faculty of Medicine, Al- Azhar University, Cairo, Egypt, Hegazyhamed91@gmail.com

Mohamed Ali Mohamed
Professor of Obstetrics and Gynecology, Faculty of Medicine, Al- Azhar University, Cairo, Egypt

Mohamed Ibrahem Mohamed Ibrahem
Lecturer of Obstetrics and Gynecology, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

How to Cite This Article

Rahman, Hamed Mohamed Hamed Abd El; Mohamed, Mohamed Ali; and Ibrahem, Mohamed Ibrahem Mohamed (2024) "A randomized, controlled trial comparing the metformin, oral contraceptive pills and their combination in patients with polycystic ovarian syndrome," *Al-Azhar International Medical Journal*: Vol. 5: Iss. 1, Article 37.
DOI: https://doi.org/10.58675/2682-339X.2209

ORIGINAL ARTICLE

A Randomized, Controlled Trial Comparing the Metformin, Oral Contraceptive Pills and their Combination in Patients With Polycystic Ovarian Syndrome

Hamed Mohamed Hamed Abd El Rahman*, Mohamed Ali Mohamed, Mohamed Ibrahem Mohamed Ibrahem

Obstetrics and Gynecology Department, Faculty of Medicine for Boys, Al-Azhar University, Cairo, Egypt

Abstract

Objectives: **To assess the effectiveness of metformin also oral contraceptive pills (OCP) in females with polycystic ovary syndrome.**

Patients and methods: **This was a prospective study that included 300 patients who were chosen at random from patients who attended outpatient obstetrics and gynecology clinics at Al-Azhar University Hospitals. Samples were obtained using a systematic random technique.**

Results: **Variations in age, BMI, and waist-to-hip ratio among the groups were statistically significant. Blood pressure, heart rate, and temperature demonstrated no statistically significant distinctions among the two groups. There was significant variance among the examined group as regard triglyceride (TG), low-density lipoprotein-cholesterol, fasting plasma glucose, and fasting insulin. There was a significant difference between before and after in group A as regards TG, and high-density lipoprotein. There were significant variations in Testosterone, dehydroepiandrosterone sulfate (DHEAS), and Android/Gynoid Fat Ratio across the groups.**

Conclusion: **According to the results of current study, females with polycystic ovary syndrome who take both OCP and metformin see considerable improvement contrasted with those who take only OCP. To corroborate our results, more research is needed with larger samples and longer follow-up periods.**

Keywords: Contraceptive pills, Metformin, Polycystic ovary syndrome

1. Introduction

Polycystic ovary syndrome (PCOS) is the endocrine condition that impacts women of reproductive years at a higher frequency than any other condition. The symptoms that are most characteristic of polycystic ovarian syndrome include hyperandrogenic chronic anovulation, dysfunctional uterine bleeding, and aberrant ovarian morphology. Polycystic ovarian syndrome may be diagnosed by observing these symptoms. PCOS is a chronic condition that can have a significant impact on a person's reproductive and metabolic health throughout their lifetime.[1]

The complex pathogenesis of polycystic ovarian syndrome precludes the development of definitive treatment guidelines. The method of therapy is modified in accordance with the patient's age and the symptoms that are currently being presented. In addition, Endocrinologists, Gynecologists, and Dermatologists have vastly different approaches to PCOS. Insulin sensitizers, antiandrogens and oral contraceptive pills (OCP) are common PCOS treatments.[2]

Accepted 26 August 2023.
Available online 8 April 2024

* Corresponding author at: Madinaty, New Cairo, Building 36 Group 34, Cairo, 11865, Egypt.
E-mail address: hegazyhamed91@gmail.com (H.M.H.A. El Rahman).

https://doi.org/10.58675/2682-339X.2209

Females with PCOS often struggle with insulin resistance. Ovarian androgen synthesis appears to be elevated when insulin resistance is coupled with increased LH secretion. In addition, the liver releases less sex hormone-binding globulin when insulin levels are high.[3]

Cardiometabolic abnormalities, such as dysglycemia, hyperlipidemia, and obesity, are common in people with polycystic ovarian syndrome. About 18%–24% of adolescents with PCOS have aberrant glucose metabolism [defined as impaired fasting glucose between 3 and 4%, impaired glucose tolerance between 13 and 15.2%, and type 2 diabetes (T2DM) within 1.5%].[4]

Adults with PCOS should be treated with OCPs to manage hyperandrogenism symptoms and contraception when pregnancy is not sought, as per recommendations made by the Endocrine Society. Metformin is only prescribed to patients who have been diagnosed with impaired glucose tolerance or other symptoms of metabolic syndrome.[5]

The goal of this research was to determine whether or not metformin and OCP were helpful for individuals with PCOS.

2. Patients and methods

This prospective observational study, include 300 patients was carefully chosen from attendee of outpatient obstetrics in addition gynecology clinics of Al Azhar University Hospitals, Samples was collected by the systematic random method.

The local ethics committee gives its stamp of approval to the research protocol, and signed informed consents are collected from all patients included in our study.

2.1. Inclusion criteria

Individuals who met the National Institute of Health (NIH) criteria for PCOS[6] (irregular or absent menstrual cycles and high levels of free or total testosterone) were included in the research. Menstrual irregularity, often known as amenorrhea, was described as having less than eight periods in a year.

2.2. Exclusion criteria

A history or current use of blood clotting disorders, stroke, breast cancer, elevated blood pressure (systolic BP $\geq$ 95th percentile on three or more occasions), severe migraines with aura and smoking (defined as over one pack of cigarettes/day for the past 6 months) are all contraindications. Additionally, other possible causes of hyperandrogenism, such as adrenal tumors, late congenital adrenal hyperplasia, as prolactinomas, have been ruled out as candidates for the condition.

2.3. Sample size

This study is based on research performed by[7] Epi-Info statically employed to determine the appropriate size of the sample by taking into account the following presumptions: a degree of confidence in both directions of 95%, with an 80% power. With a margin of error of 5%, the odds ratio is determined to be 1.115. The Epi-Info output allowed for a maximum sample size of 282. Because of this potential for attrition during follow-up, the sample size was expanded to 300 people.

2.4. Methods

Every patient was then categorized into one of these three groups: 100 patients in the group (A) were given OCP treatment. Metformin was administered to each of the 100 participants in group B. One hundred patients were assigned to the group C treatment, which consisted of OCP and Metformin.

All patients subjected to: each individual gave their consent after being given information. Full documentation of historical events: personal history, the history of any complaints, the history of obstetrics and menstruation, the history of prior medical treatment and past surgical treatment, as well as family history.

Complete checkup and assessment of the body Examination of the patient's vital signs, including blood pressure, temperature, heart rate (HR), and respiratory rate, as well as symptoms of pallor, jaundice, cyanosis, and enlargement of the lymph nodes.

Estimation of the time when menopause will occur. The metformin dosage was raised from 500 mg/day to 2000 mg/day over the course of a month. The OCP consisted of the conventionally dosed combination of 35 mcg ethinyl estradiol also 2 mg cyproterone acetate. We will determine level of free and total testosterone through-out the study and detection of amenorrhea. Patients were monitored for a full 6 months, involving monthly visits to the outpatient department.

2.5. Statistical analysis

The data will be inserted into the SPSS system (Statistical Package for the Social Sciences) version 26.0 and Microsoft Excel 2016 for tabulation and

statistical analysis. Quantitative variables were subjected to inferential analysis through the independent *t*-test for parametric data and the Mann–Whitney *U* for nonparametric data between two independent groups. The χ^2 test for separate groups was employed for inferential analysis of qualitative data. Nonparametric variables between pairs of samples were tested for statistical significance utilizing the Wilcoxon Rank test.

3. Results

The demographic features of the two different groups are compared in (Table 1). The mean age in group A, B, and C was 22.5 ± 1.8, 22.9 ± 1.98, and 22.7 ± 1.5 years, respectively. The mean BMI in group A, B as well as C was 27.5 ± 1.8, 28.9 ± 1.98, and 31.7 ± 1.5 years, respectively. The mean Waist circumference in group A, B, and C was 89.5 ± 7.6, 93.10 ± 9.6, and 98.10 ± 9.5 years respectively. The mean Waist-hip ratio in group A, B, and C was 0.88 ± 0.06, 0.91 ± 0.07, and 0.93 ± 0.08 years, respectively. There were statistically significant variations in age, BMI, and waist-to-hip ratio among the two groups shown in (Table 1).

When comparing the two groups' systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, and temperature readings, there was no statistically significant difference between them that showed in (Table 2).

There was significant difference among studied group as regard triglyceride (TG), low-density lipoprotein-cholesterol, fasting blood sugar and fasting insulin. There was significant difference among before and after in group A concerning TG, high-density lipoprotein that showed in (Table 3).

Table 1. Demographic characteristics among the examined groups.

	Group A ($n = 100$)	Group B ($n = 100$)	Group C ($n = 100$)	Test value	*P*-value
Age (y) Mean ± SD	22.5 ± 1.8	22.9 ± 1.98	22.7 ± 1.5	F = 7.58	**0.02**
BMI Mean ± SD	27.5 ± 1.8	28.9 ± 1.98	31.7 ± 1.5	F = 7.58	**0.02**
Waist circumference Mean ± SD	89.5 ± 8.6	93.10 ± 9.6	98.10 ± 9.5	1.41	0.49
Waist-hip ratio Mean ± SD	0.88 ± 0.06	0.91 ± 0.07	0.93 ± 0.08	8.060	**0.017**

***P* value less than 0.05:** is significant, ***P* value less than 0.01:** is highly significant.
ANOVA, X^2, Chi- Square test; **SD,** Standard deviation.

Table 2. Clinical data collected from each of the groups that were studied.

	Group A ($n = 100$)	Group B ($n = 100$)	Group C ($n = 100$)	Test value	*P*-value
SBP Mean ± SD	115.5 ± 5.8	115.9 ± 5.98	115.7 ± 5.5	F = 0.70	0.70
DBP Mean ± SD	74.5 ± 4.8	74.9 ± 4.98	74.7 ± 4.5	F = 1.02	0.59
Temperature Mean ± SD	37.01 ± 0.1	37.05 ± 0.12	37.06 ± 0.13	1.41	0.49
HR Mean ± SD	75.0 ± 2.0	76.0 ± 2.0	77.0 ± 2.0	0.0	1.0

Table 3. Comparison amongst both groups concerning laboratory results.

	Group A ($n = 50$)	Group B ($n = 50$)	Group C ($n = 50$)	Test value	*P*-value
Before TC, mg/dL	159.8 ± 31.6	164.1 ± 37.4	195.9 ± 38.5	4.3	0.11
After	163.8 ± 33.2	160.1 ± 35.4	192.9 ± 36.4	0.86	0.64
P	0.62	0.58	0.57		
Before TG, mg/Dl	113.13 ± 30.23	135.12 ± 49.27	175.12 ± 68.21	59.7	**0.0004**
After	130.2 ± 40.5	130.2 ± 42.3	170.3 ± 62.4	23.7	**0.00006**
P	**0.003**	0.13	0.37		
Before LDL-cholesterol, mg/Dl	96.1 ± 21.8	94.9 ± 27.0	115.0 ± 30.01	16.29	**0.002**
After	95.1 ± 20.77	97.6 ± 30.12	111.0 ± 27.2	13.6	**0.001**
P	0.63	0.27	0.32		
Before HDL-cholesterol, mg/Dl	41.3 ± 10.0	39.4 ± 9.8	41.6 ± 11.5	3.07	0.21
After	39.9 ± 7.0	41.2 ± 10.3	41.9 ± 11.1	21.70	**0.0001**
P	**0.0004**	0.6215	0.72		
Before Fasting plasma glucose, mg/Dl	88.5 ± 7.22	90.4 ± 10.7	98.0 ± 40.5	306.06	**0.00001**
After	94.5 ± 8.5	88.2 ± 9.5	94.2 ± 37.4		
P	0.106	0.23	0.42		
Before Fasting insulin, μIU/Ml	13.3 ± 5.2	14.55 ± 7.1	17.8 ± 8.8	26.14	**0.0002**
After	14.1 ± 5.7	12.4 ± 6.5	15.7 ± 7.5	7.40	**0.02**
P	0.36	0.38	0.11		

TG, triglyceride.

Table 4. Comparison amongst the examined groups regarding different biochemical parameters.

	Group A ($n = 50$)	Group B ($n = 50$)	Group C ($n = 50$)	Test value	*P*-value
Before Testosterone, ng/ml	0.8 ± 0.12	0.86 ± 0.19	0.75 ± 0.11	36.24	**0.000001**
After	0.65 ± 0.08	0.80 ± 0.11	0.61 ± 0.09	10.4	**0.005**
P	**0.00007**	**0.0000001**	**0.047**		
Before DHEAS, μg/dl	265.12 ± 56.3	232.2 ± 45.2	222.5 ± 40.46	11.41	**0.003**
After	231.2 ± 48.35	215.4 ± 36.5	195.1 ± 32.41	17.2	**0.00018**
P	0.131	**0.034**	**0.02**		
Before Percentage android/percentage gynoid fat	0.96 ± 0.10	0.95 ± 0.11	0.95 ± 0.13	7.07	**0.029**
After	0.99 ± 0.12	0.94 ± 0.10	0.94 ± 0.12	4.17	0.123
P	0.071	0.34	0.42		

DHEAS, dehydroepiandrosterone sulfate.

There was significant variance amongst before and after in group A as regard Testosterone. There was significant difference amongst before as well as after in group B as regard Testosterone, dehydroepiandrosterone sulfate (DHEAS). There was significant change among before and after in group C as regard Testosterone, DHEAS. There was significant difference among studied group concerning Testosterone, DHEAS and Percentage android/percentage gynoid fat that showed in (Table 4).

4. Discussion

This prospective observational study included 300 individuals who were selected from Al Azhar University Hospitals outpatient obstetrics and gynecology clinic attendees. Samples were collected using a systematic random procedure. Participants were separated into three groups: group (A): oral contraceptive pills was administered to 100 patients. 100 cases in group B were treated with Metformin. One hundred patients were administered OCP and Metformin in group (C). The length of the investigation varied between 6 and 12 months.

Concerning the distribution of several demographic factors among the groups that were studied, the mean age in group A, B, also C was 22.5 ± 1.8, 22.9 ± 1.98 and 22.7 ± 1.5, years respectively. The mean BMI in group A, B, and C was 27.5 ± 1.8, 28.9 ± 1.98, and 31.7 ± 1.5 years, respectively. The mean Waist circumference in group A, B as well as C was 89.5 ± 7.6, 93.10 ± 9.6, and 98.10 ± 9.5 years, respectively. The mean Waist-hip ratio in group A, B, and C was 0.88 ± 0.06, 0.91 ± 0.07 and 0.93 ± 0.08 years, respectively. There was statistically significant difference between the studied groups relating to age, BMI and Waist-hip ratio.

This research comprised ninety people who had just been diagnosed with PCOS (ages 18–40, premenopausal, symptom duration above 6 months and normal thyroid function). The participants were assigned to one of three groups at random: group 1 (OCP), group 2 (Metformin), or group 3 (Metformin + OCP) based on the treatment that was administered to them. Group 1 got the oral contraceptive pill. The average age of the participants was 23.2 years, with a standard deviation of 4.4 years, and their BMI ranged from 28.4 to 6.1 kg/m^2. There was not a significant difference in age across the groups; however, there were variations in waist-to-hip ratio and BMI.[7]

Patients were randomly assigned to receive either metformin (1000 + 1000 mg/d) or OCP (150 mg desogestrel+30 μg ethinylestradiol) for a period of one year. Moreover[8] observed different results and reported that patients received either treatment. The patients' ages as well as their BMI were comparable across all three treatment groups.

The current study demonstrated that with reference to clinical data between the two groups that were evaluated. The mean SBP for group A was 115.5 with a standard deviation of 5.8, 115.9 with a standard deviation of 5.98, and 115.7 with a standard deviation of 5.5. In groups A, B, and C, respectively, the mean DBP was 74.5 ± 4.8, 74.9 ± 4.98, and 74.7 ± 4.5. The mean temperature in group A, B, and C was 37.01 ± 0.1, 37.05 ± 0.12, and 37.06 ± 0.13, respectively. The mean HR in group A, B, and C was 75.0 ± 2.0, 76.0 ± 2.0, and 77.0 ± 2.0, respectively. There was no statistically significant difference in either the SBP or DBP, HR, or temperature between the two groups of people.

Our outcomes were sustained by study of[7] as Clinical presentation and symptomatology were observed to be similar among the three groups.

However, in the study of[9] the 98 people who were assessed, 23 were assigned to receive either a placebo (the OC group) or metformin in addition to OC (the Met-OC group). When compared to the OC group, the Met-OCs had somewhat higher blood pressure.

The current study showed that as regard Laboratory measures; there were significant difference between studied group as regard TG, low-density lipoprotein-cholesterol, fasting plasma glucose and

fasting insulin. There was significant difference between before and after in group A as regard TG, high-density lipoprotein.

In the study of[10] they found that 117 teenage females with PCOS were randomly allocated to one of three groups: metformin, combined oral contraceptive pills (COC), or control. Group A received metformin, group B COC, and group C placebo. Insulin levels during fasting and after a load dropped significantly in group A, from 18.3 ± 3 μIU/l and 126 ± 43 μIU/l to 10 ± 3 and 64 ± 15, respectively. In the same group, insulin sensitivity increased from 4.1 ± 0.3 μIU/l to 4.6 ± 0.5 μIU/l, which may be measured by GIR. In group B, fasting and after-load insulin rose from 15 ± 3 and 103 ± 91 μIU/l to 19 ± 4 and 187 ± 22. Insulin sensitivity decreased when the glucose-insulin ratio dropped from 4.4 ± 0.2 to 3.1 ± 0.3. In group C, fasting insulin rose from 15 ± 2 to 22 ± 3, load insulin increased nonsignificantly from 100 ± 21 to 111 ± 12, and the ratio of glucose to insulin decreased from 3.9 ± 0.5 to 3.1 ± 0.3, indicating insulin resistance.

The Rotterdam criteria were used to identify 40 women with PCOS in Ref. 11 randomized clinical study in Turkey for 90 days, they took metformin (1700 mg/d) with an oral contraceptive pill (ethinylestradiol 35 μg with cyproterone acetate 2 mg) or the OCP alone. Metformin and oral contraceptive pills reduced BMI by 4.3% and 4.6%, respectively ($P < 0.001$). Groups created lipid profiles. Metformin + oral contraceptive pills and oral contraceptive pills alone reduced insulin levels (3.2 and 2.4 μIU/ml, respectively, $P < 0.001$).[11]

Our results showed that there was significant variance between Prior to and following in group A as regard Testosterone. There was significant change among before and after in group B as regard Testosterone, DHEAS. There was significant variance amongst before and after in group C as regard Testosterone, DHEAS. There was significant alteration among studied group as regard Testosterone, DHEAS and Percentage android/percentage gynoid fat.

While in the study of[7] the evidence points to OCP lowering hirsutism, reducing IR, and raising body fat percentage. Hyperandrogenism, dyslipidemia, inflammation, and body fat have all been lowered via the use of metformin alone. The combined group's findings are consistent with those of group 2. After 6 months of intervention and lifestyle guidance, the body weight of the three groups was not statistically different from one another. There is a clear tendency toward altering the patient's metabolic environment as a result of metformin treatment. Metformin has been demonstrated to be as effective as OCP in reestablishing a regular menstrual cycle, contradicting the results of several earlier trials.[4]

In the study of[10] he found that Metformin and COC significantly improved cycle regularity (36/40 & 40/40, respectively; 92.5% and 100%) and subjective hirsutism (10/40 and 16/40; 25% and 40%). The control group exhibited no change in these characteristics. The mean blood testosterone level in group A (metformin) dropped from 1.5 ± 0.4 to 0.8 ± 0.1 g/ml after 6 months of medication. The mean blood testosterone level declined to 1.2 ± 0.3 g/ml over the follow-up period, which was not statistically significant. Group B (COC) had the lowest blood testosterone at the end of the 2-year experiment (0.7 0.2 g/ml versus 1.3 0.5 g/ml). The increase in mean serum testosterone from 1.2 to 1.5 ± 0.4 g/ml in group C was not statistically significant. The growth was insignificant.[10]

Whereas in meta-analysis conducted by[12] 56 different studies met the requirements to be considered for inclusion. In adolescents with evidence of inadequate quality, meta-analyses showed that metformin was superior to COCP in terms of BMI [mean difference (MD) −4.02 (−5.23, −2.81), $P < 0.001$]; however, COCP was superior to metformin in terms of menstrual regulation [MD −0.19 (−0.25, −0.13), $P < 0.00001$].[12]

While[9] after 3 months, it was found that: (1) Met-OC, but not OC, decreases BMI and free testosterone; (2) Met-OC and OC affect insulin sensitivity, serum inflammatory markers, and lipid profile similarly; and (3) Met-OC improves endothelial function better than OC monotherapy.[9]

Furthermore[13] stated that at the 3-month follow-up, nine of the 16 individuals on metformin and all 17 individuals on the analyzed oral contraceptives containing drospirenone had achieved regular menstrual cycles ($P = 0.002$ among two groups); at the 6-month follow-up, eight of the 11 individuals on metformin and the 11 patients on the analyzed oral contraceptives containing drospirenone had achieved regular menstrual cycles ($P = 0.06$ among the two groups). At the 6-month follow-up, there was not a statistically significant distinction among both groups in terms of BMI or blood testosterone levels.

4.1. Conclusion

Our study has shown that adding metformin to OCP results in much more favorable outcomes for patients with PCOS than using OCP by alone. Our findings need to be validated by other studies with larger trials and more extensive follow-up period.

Funding

No funds: yes.

Conflicts of interest

There are no conflicts of interest.

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