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Hanaa Fathi Abo Ria
Department of Obstetrics and Gynecology, Faculty of Medicine for girls, Al-Azhar University, Cairo, Egypt.

Hanan Abd El-Monem Mohammed
Department of Obstetrics and Gynecology, Faculty of Medicine for girls, Al-Azhar University, Cairo, Egypt.

Hoda Ismail Sayed Hemida
Department of Obstetrics and Gynecology, Faculty of Medicine for girls, Al-Azhar University, Cairo, Egypt., ismailhoda101@yahoo.com

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ORIGINAL ARTICLE

Effect of Metformin and Myoinositol in Patients with Polycystic Ovary Syndrome

Hanaa Fathi Abo Ria, Hanan Abd El-Monem Mohammed, Hoda Ismail Sayed Hemida*

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

Abstract

Background: **Polycystic ovary syndrome (PCOS), also known as Stein−Leventhal syndrome, is a reproductive hormone condition. It causes irregular ovulation, nonexistent periods, insulin resistance, and androgenic hormone overproduction. Hormonal imbalances may cause extra hair growth, acne, hair loss, and greasy skin. If you suspect PCOS, visit a doctor. It may have a major influence on your health.**

Aim: **To determine the adjuvant effect of metformin and myoinositol (MI) in PCOS patients.**

Patients and methods: **This research was performed on three subgroups of 100 women with PCO (according to the Rotterdam criteria, ESHRE/ASRM 2004). Group I (50 women): who received metformin (500 mg + 2 gm MI) in the evening for 3 months. Group II (50 women): obtained metformin 500 mg (cidophage 500 mg) three times daily for 3 months. All females involved in the research submitted full history (personal, medical, menstrual, and general) and physical examination.**

Result: **There was no statistically significant distinction in the baseline characteristics of both groups. Transvaginal ultrasonography of 'ovarian size' posttreatment showed a statistically significant distinction among both the groups in terms of normal ovarian size. The variance in pregnancy rates among the two groups was statistically highly significant. Also there was a statistical significant correlation among pregnancy rates according to transvaginal ultrasound regarding ovarian size in all patients.**

Conclusion: **We found that combination of metformin with MI give better results in PCOS than metformin alone.**

Keywords: Metformin, Myoinositol, Polycystic ovary syndrome

1. Introduction

Five to 15 % of reproductive-age women are affected with polycystic ovary syndrome (PCOS), making it one of the most prevalent endocrine disorders[1] (see Figs. 1 and 2).

In spite of the impact of genetic and environmental factors, the precise origin of PCOS, the most common endocrine illness seen in females of reproductive age, continues to be unknown. PCOS is the condition that affects more women than any other conditions. A large number of studies have been carried out to explore the distribution and composition of fat in women who have PCOS. PCOS has been linked to increased quantities of visceral adipose tissue as well as overall adiposity, which may boost the risk of obesity, cardiovascular disease, insulin resistance, and type 2 diabetes in women with PCOS regardless of their weight status. This highlights the need of further research into the pathogenesis of PCOS as well as the development of effective treatment approaches.[2]

The disease is often compounded by metabolic abnormalities in other tissues, which raises the risk of cardiovascular disorders and endometrial cancer. As a consequence, the patients' life, mental, and physical health are significantly impacted. Nowadays, oral contraceptives and insulin are the most common clinical treatments for PCOS, although the efficacy of these medications is inadequate.[3]

Clomiphene citrate (CC) was the main medication used to stimulate ovulation in these individuals, but it had a high incidence of failure. Nevertheless,

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* Corresponding author. Department of Obstetrics and Gynecology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, 11651, Egypt.
E-mail address: ismailhoda101@yahoo.com (H.I.S. Hemida).

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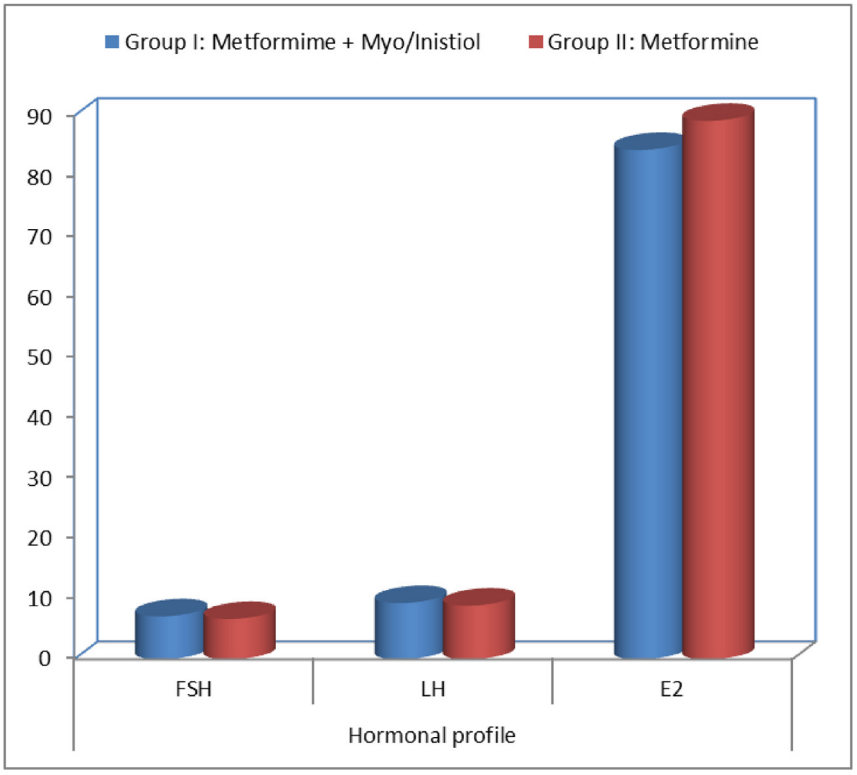

Fig. 1. Bar chart between group I and group II according to hormonal profile.

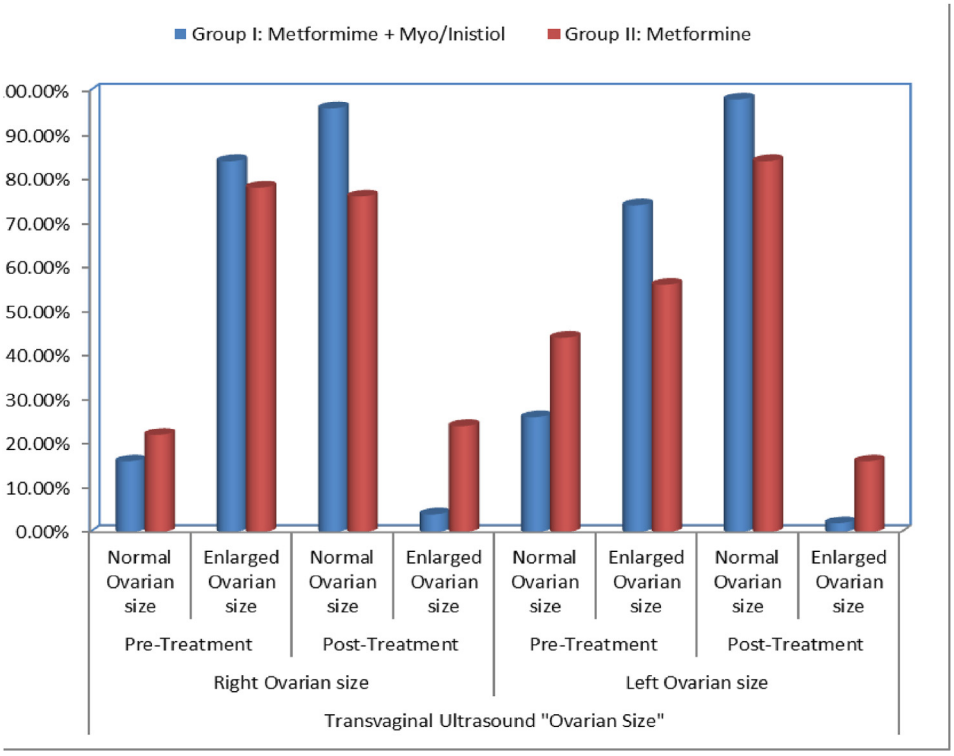

Fig. 2. Bar chart between group I and group II according to transvaginal ultrasound 'ovarian size.'

individuals who used CC for more than six cycles had an elevated risk of ovarian cancer.[4]

In contrast to laparoscopic ovarian drilling (LOD) therapy, CC treatment has shown a disparity in ovulation rates (75–80 %) and conception rates (30–40 %) in females with CC-resistant PCOS.[5]

The disparity may continue to some degree even with gonadotropin therapy.[5] Insulin-sensitizing drugs have been investigated as potential treatments for the underlying cause of insulin resistance disorders.

Although hyperinsulinemia plays a substantial role in anovulation in women with PCOS, a drop in serum insulin concentrations is likely to result in clinical benefits. In obese women with PCOS, a decrease in hyperinsulinemia ameliorates the symptoms, particularly ovulation and pregnancy rate.[6]

Metformin did not enhance live birth rates whether taken alone, in combination with clomiphene, or as an alternative to clomiphene, according to a recent analysis conducted by Cochrane. While the use of metformin was related with greater rates of clinical pregnancy and ovulation, this was not the case when the drug was used. This implies that although metformin may have some advantages in enhancing specific elements of fertility, it may not be the best effective treatment choice for all women who are experiencing with infertility and seeking a solution to their problem. There is a pressing need for more investigation into the most successful methods of infertility treatment for women who are afflicted with a variety of underlying disorders.[7] Consequently, it is necessary to discover treatment solutions for treating PCOS in females.

The role of inositol-phosphoglycan (IPC) mediators of insulin action has received increased attention throughout the last decade. Insulin-resistant PCOS women have been shown to have a deficiency in myoinositol (MI). The alteration in ovarian inositol metabolism in PCOS is due to hyperinsulinemia, which is induced by the underlying insulin resistance in PCOS. Due to faster MI to D-chiro-inositol (DCI) epimerization in the ovary, hyperinsulinemic people with PCOS tend to have a greater DCI/MI ratio (i.e. overproduction of DCI). Reducing MI increases the isoform DCI and promotes androgen production. In women with PCOS, the vitamin B complex cofactor and insulin sensitizer MI improves insulin signaling, reduces blood insulin, and decreases serum testosterone to restore normal ovulatory activity.[8]

2. Patients and methods

The outpatient department of AL-Zahraa University Hospital and El-Sheikh Zayed Hospital hosted a prospective randomized trial from May 2017 to December 2017. After the local ethics committee approved the study, 100 women who visited the infertility outpatient clinic provided written informed consent.

Participating in the study were 100 women who had been diagnosed with PCOS using the Rotterdam criteria set in 2004 by the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine. In group I, there were 50 people who took metformin (500 mg) and MI (2 g) once a day in the evening for 3 months. In group II, there were 50 people who took metformin (500 mg) three times a day for the same amount of time.

The inclusion criteria: age: 18–40 years, women with PCOS (ultrasonographic evidence of anovulation, oligo-ovulation, or hyperandrogenism; the existence of 12 or more follicles 2–9 mm in diameter; and/or at least one enlarged ovary ($4 \times 10\ cm^3$); and no history of CC resistance among the patients).

Exclusion criteria: age: less than 18 or more than 40 years, sonohysterography or hysteroscopy for women with a uterine cavity abnormality, sperm analysis for the male factor. Individuals who had taken any hormonal medicines (nonprogesterone withdrawal hemorrhage) in the 3 months before the trial were also excluded, as were those who had ovarian cysts or an allergy to the pharmaceuticals administered.

2.1. Methods

All females involved in the research submitted full history (personal, medical, menstrual, and general) and physical examination.

2.2. Technique of ultrasound examination

To assess follicular quantity, size, endometrial thickness and pattern, and follicular rupture, transvaginal ultrasonography was performed every other day beginning on cycle day 9 and continuing until ovulation. At least one follicle larger than 18–20 mm is needed for ovulation to occur. Its follicular size corresponds to a time when endometrial thickness is at its maximum. At 18–20 mm, the dominant follicle is injected with 10 000 IU of HCG intramuscularly, and sexual activity should be timed accordingly. In situations where pregnancy was not a factor, treatment was cycled back in for a total of three rounds. The main outcome measured was the existence of a gestational sac that contained fetal hearts, as established by ultrasonography, which was considered to be the defining characteristic of a naturally occurring

clinical pregnancy. Other factors, such as the frequency and timing of ovulation, the thickness and pattern of the endometrial lining, the number and size of follicles, including the total count of follicles, and the pattern of the endometrial lining were also considered. All these factors were taken into consideration.

2.3. Statistical analysis

The Statistical Package for the Social Sciences, version 20.0 was used to conduct an analysis on the data that was acquired for this research, and the results of that analysis are shown below (SPSS Inc., Chicago, Illinois, USA). The collected quantitative data were provided in the form of mean values together with their associated SD, while the obtained qualitative data were presented in the form of frequencies and percentages of occurrences, respectively.

3. Results

This table demonstrated that there was not a discernible variance among the two groups in terms of their starting features; more specifically, there was not a statistically significant gap among the findings of both groups (Tables 1–6).

4. Discussion

PCOS may manifest itself in a wide variety of ways, including irregular periods, high testosterone levels, ovarian dysfunction, insulin resistance, and extra body fat. These are just a few of the potential symptoms. The pathogenesis of hyperandrogenism in PCOS is significantly influenced by hyperinsulinemia. This is because hyperinsulinemia stimulates the production of androgen in the ovaries and adrenal glands, as well as the production of sex hormone binding globulin and insulin-like growth factor binding protein 1 in the liver. Both of these processes take place in the liver.

Anovulation and follicular atresia in premenopausal women are caused by elevated androgen signaling. Obese people had higher insulin resistance and reactive hyperinsulinemia after adipose tissue stimulation.[9]

According to our findings, there was no statistically significant distinction in the baseline characteristics of both groups.

In a meta-analysis it was found that 684 people took part in the research that compared metformin with MI therapy for diabetes treatment, with 352 receiving metformin and 331 receiving MI. Each

Table 2. Comparison among group I and group II according to hormonal profile pretreatment.

Hormonal profile	Group I	Group II	*t*-test	*P* value
FSH				
Mean ± SD	7.10 ± 2.31	6.66 ± 2.23	0.920	0.340
Range	1.3–14.2	1.3–13.4		
LH				
Mean ± SD	9.30 ± 3.32	8.89 ± 4.11	0.299	0.586
Range	1.1–14.3	1.1–16.7		
E2				
Mean ± SD	84.36 ± 12.91	89.18 ± 22.76	1.694	0.196
Range	62.4–103.5	50–216		

According to the data shown in this table, there was no significant variation in the hormonal profiles of the two groups.
E2, estradiol; FSH, follicular-stimulating hormone; LH, luteinizing hormone.

Table 1. Comparison of group I and group II based on their initial characteristics.

Baseline characteristics	Group I: metformim + myoinistiol ($N = 50$)	Group II: metformin ($N = 50$)	Test	*P* value
Age (years)				
Mean ± SD	26.42 ± 4.61	26.80 ± 4.67	$t = 0.167$	0.683
Range	18–35	18–36		
Menstrual history [*n* (%)]				
Regular	11 (22)	18 (36)	$\chi^2 = 2.38$	0.123
Irregular	39 (78)	32 (64)		
Parity				
Median (IQR)	0 (1)	1 (1)	$Z = 0.163$	0.688
Range	0–1	0–2		
Abortion				
Median (IQR)	1 (1)	1 (2)	$Z = 0.844$	0.361
Range	0–2	0–6		
Duration of marriage (years)				
Mean ± SD	1.90 ± 0.81	1.73 ± 1.19	$t = 0.743$	0.391
Range	1–3.5	0.5–6		

IQR, interquartile range; *t*, independent sample *t*-test; *Z*, Mann–Whitney test; χ^2, χ^2 test.
P value more than 0.05 NS.

Table 3. Comparison between group I and group II according to transvaginal ultrasound 'follicular count'.

Transvaginal ultrasound 'follicular count'	Group I	Group II	*t*-test	*P* value
Right ovary				
Pretreatment				
Mean ± SD	15.07 ± 2.68	14.29 ± 2.07	1.629	0.107
Range	12–18	12–17		
Posttreatment				
Mean ± SD	11.71 ± 1.92	12.94 ± 1.87	3.245	0.002*
Range	10–14	10–15		
Left ovary				
Pretreatment				
Mean ± SD	15.24 ± 2.01	15.71 ± 1.99	1.175	0.243
Range	12–19	13–18		
Posttreatment				
Mean ± SD	11.34 ± 1.81	12.45 ± 1.93	2.966	0.004*
Range	10–13	10–14		

This table showed that there was a statistical significant improved number of follicular count right and left in each group, but group I significantly improved more than group II.
P value more than 0.05 NS; **P* value less than 0.05 S.

Table 4. Comparison between group I and group II according to transvaginal ultrasound 'ovarian size'.

Transvaginal ultrasound 'ovarian size'	Group I [*n* (%)]	Group II [*n* (%)]	χ^2	*P* value
Right ovarian size				
Pretreatment				
Normal ovarian size	8 (16)	11 (22)	0.260	0.612
Enlarged ovarian size	42 (84)	39 (78)		
Posttreatment				
Normal ovarian size	48 (96)	38 (76)	6.728	0.009*
Enlarged ovarian size	2 (4)	12 (24)		
Left ovarian size				
Pretreatment				
Normal ovarian size	13 (26)	22 (44)	3.560	0.059
Enlarged ovarian size	37 (74)	28 (56)		
Posttreatment				
Normal ovarian size	49 (98)	42 (84)	4.396	0.036*
Enlarged ovarian size	1 (2)	8 (16)		

According to the results of the transvaginal ultrasound that were performed after treatment, the table revealed that there was a statistically significant difference among group I and group II in terms of 'ovarian size.' The results of the ultrasound were shown in the table.
P value more than 0.05 NS; **P* value less than 0.05 S.

study had a different treatment length, from 12 weeks to 6 months. Patients who took metformin were not significantly younger than those who received MI ($P = 0.77$); the average age of both groups was 23.96. The mean BMI of the metformin and MI groups was 25.71 and 25.14, respectively ($P = 0.97$), hence there was no statistically significant difference among the two.[10]

Table 5. Comparison between group I and group II according to results of treatment with insulin sensitizer.

Pregnancy rate	Group I [*n* (%)]	Group II [*n* (%)]	χ^2	*P* value
Pregnant	38 (76)	27 (54)	5.319	0.021
Non pregnant	12 (24)	23 (46)		

This table showed that there was highly statistically significant variance regarding pregnancy rate between both groups.

There was no statistical significant difference between both the groups according to hormonal profile.

According to Jaura et al.,[11] there was no statistically significant decline in luteinizing hormone/follicular-stimulating hormone among the two groups ($P > 0.05$).

There was statistical significant improved number of follicular count right and left in each group, but group I significant improved than group II, with *P* value less than 0.05 S.

According to Chhabra and Malik[12] the antral follicle count (AFC) had a statistically significant variance in all three groups in the beginning, with the largest AFC in the MI-only group. Hence, it was hypothesized that insulin sensitizer medications, such as metformin and MI, would lower insulin

Table 6. Association between pregnancy rate according to all parameters in all patients.

All patients	Pregnant ($N = 65$)	Nonpregnant ($N = 35$)	$t/\chi^{2\#}$	P value
Demographic data				
Age (years)	26.72 ± 5.06	26.40 ± 3.73	$t = 0.110$	0.741
Menstrual history [n (%)]				
Regular	17 (26.2)	12 (34.3)	$\chi^2 = 0.389$	0.533
Irregular	48 (73.8)	23 (65.7)		
Parity	0.28 ± 0.52	0.29 ± 0.46	$t = 0.007$	0.933
Abortion	0.58 ± 1.00	0.40 ± 0.55	$t = 1.024$	0.314
Duration of marriage (years)	1.94 ± 1.12	1.58 ± 0.73	$t = 2.921$	0.091
Hormonal profile				
FSH	6.94 ± 2.32	6.77 ± 2.22	$t = 0.115$	0.735
LH	8.74 ± 3.83	9.76 ± 3.46	$t = 1.732$	0.191
E2	84.40 ± 13.22	91.17 ± 25.38	$t = 3.082$	0.082
Transvaginal ultrasound				
Follicular count				
Pretreatment right ovary	15.37 ± 1.93	15.46 ± 1.42	$t = 0.243$	0.809
Pretreatment left ovary	15.51 ± 1.46	15.77 ± 1.95	$t = 0.753$	0.453
Posttreatment right ovary	12.59 ± 1.07	13.73 ± 1.17	$t = 4.918$	<0.001**
Posttreatment left ovary	12.35 ± 1.02	14.18 ± 1.19	$t = 8.067$	<0.001**
Ovarian size [n (%)]				
Pretreatment right ovarian size				
Normal ovarian size	15 (23.1)	4 (11.4)	$\chi^2 = 1.320$	0.251
Enlarged ovarian size	50 (76.9)	31 (88.6)		
Posttreatment right ovarian size				
Normal ovarian size	35 (53.8)	3 (8.6)	$\chi^2 = 17.918$	<0.001**
Enlarged ovarian size	30 (46.2)	32 (91.4)		
Pretreatment left ovarian size				
Normal ovarian size	23 (35.4)	12 (34.3)	$\chi^2 = 0.012$	0.913
Enlarged ovarian size	42 (64.6)	23 (65.7)		
Posttreatment left ovarian size				
Normal ovarian size	42 (64.6)	6 (17.1)	$\chi^2 = 18.683$	<0.001**
Enlarged ovarian size	23 (35.4)	29 (82.9)		

This table showed that there was a statistical significant correlation among pregnancy rates according to transvaginal ultrasound regarding ovarian size in all patients.

E2, estradiol; FSH, follicular-stimulating hormone; LH, luteinizing hormone.

P value more than 0.05 NS; *P value less than 0.05 S; **P value less than 0.001 HS.

resistance and, subsequently, hyperandrogenism, serum AMH levels, and D2–AFC and transform anovulatory PCO patients into ovulatory patients. The adjusted hormonal and metabolic environment was hypothesized to enhance responsiveness to stimulation in future IVF cycles. There was statistical significant higher normal ovarian in group I compared with group II according to transvaginal ultrasound 'ovarian size' in posttreatment.

Ovarian volume on the right and left sides of the body showed no statistically significant variance among the three groups in a prospective, randomized, comparative investigation with MI, metformin, or both.[13]

The pregnancy rate was significantly higher in group I than in group II, and the difference was statistically significant.

In Chirania et al.[13] they found that 66.66 % of patients in group I, which was treated with 1 g/day of MI, claimed alleviation from menstruation problems, while 57.14 % of patients who suffered from infertility reported becoming pregnant as a result of the treatment. On the other hand, in group II, where patients were given 1 g of metformin per day, only 15.78 % of the cases with menstruation problems showed improvement, whereas 100 % of the cases with infertility reported a pregnancy.

Ramanan et al.[14] also discovered that after taking MI, both basal insulin levels and the HOMA index dropped considerably.

There was a statistical significant association between the pregnancy rate according to transvaginal ultrasound regarding ovarian size in group I.

MI is often the first line of defense in treating and preventing disorders like PCOS.[15] MI is a six-hydroxyl group cyclic carbohydrate that has multiple metabolic functions in the body.[16]

Transvaginal ultrasonography revealed a statistically significant correlation among ovarian size and the likelihood of pregnancy in group II.

Transvaginal ultrasound measurements of ovarian size were correlated with an increased likelihood of conception in all individuals.

According to the findings of Hasan and Abd El Hameed, using metformin resulted in a significant reduction in the volume of the average ovary. Since a favorable correlation between ovarian volume and BMI was discovered, the results of the ultrasound may be connected to anthropometric parameters.[17]

5. Conclusions

Regarding our results combination of metformin and MI give better results and improvement of ovarian activity in PCOS patients than metformin only.

Conflicts of interest

There are no conflicts of interest.

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