Clinical Investigation / Araştırma

DOI: 10.4274/tjod.galenos.2024.21456

Turk J Obstet Gynecol 2024;21:78-84

Comparison of metformin, myoinositol and metformin-myoinositol combined treatments for polycystic ovary syndrome

Polikistik over sendromunda metformin, miyoinozitol ve metformin-miyoinozitol kombine tedavilerinin karşılaştırılması

Ceyda Karadağ[1], Mehmet Sakinci[2], Özer Birge[3], Mehmet Sait Bakır[4], Burak Karadağ[5], Saliha Sağnıç[6]

[1]*Antalya City Hospital, Clinic of Gynecologic Oncology, Antalya, Turkey*

[2]*Akdeniz University Faculty of Medicine, Department of Obstetrics and Gynecology, Antalya, Turkey*

[3]*Ordu Training and Research Hospital, Clinic of Gynecologic Oncology, Ordu, Turkey*

[4]*Hatay Training and Research Hospital, Clinic of Gynecologic Oncology, Hatay, Turkey*

[5]*University of Health Sciences Turkey, Antalya Training and Research Hospital, Clinic of Obstetrics and Gynecology, Antalya, Turkey*

[6]*University of Health Sciences Turkey, Van Training and Research Hospital, Clinic of Gynecologic Oncology, Van, Turkey*

**This study was Dr. Ceyda Karadag's specialization thesis.*

Abstract

Objective: The objective of this study was to assess the effectiveness of myoinositol (4 g myoinositol + 400 mcg folic acid/day) compared with metformin (average 1700 mg/day), as well as the combined efficacy of both treatments in managing insulin-resistant polycystic ovary syndrome (PCOS) among women.

Materials and Methods: We retrospectively analyzed the records of 68 reproductive-age PCOS patients with insulin resistance over a 3-month period. Oral glucose tolerance tests (OGTT) (75 gr) were conducted to measure glucose levels at 0 and 120 min. Moreover, changes in prolactin, thyroid stimulating hormone, high-density lipoprotein, low-density lipoprotein, triglyceride levels, total cholesterol, follicle-stimulating hormone, luteinizing hormone, total testosterone, free testosterone, and dehydroepiandrosterone sulfate (DHEA-S) levels were evaluated pre- and post-treatment over a 3-month period.

Results: Statistically significant improvements were observed in menstrual regularity, body mass index (BMI), modified Ferriman Gallwey scores, OGTT glucose levels at 0 and 120 min, total testosterone, free testosterone, and DHEA-S levels across all groups ($p<0.005$).

Conclusion: No significant variances were observed in terms of BMI, modified Ferriman Gallwey scores, or androgen levels across the three treatment cohorts. The combination of myoinositol and metformin did not confer additional benefits compared with either treatment alone.

Keywords: Hirsutism, insulin resistance, metformin, myoinositol, polycystic ovary syndrome

Öz

Amaç: Bu çalışmada, polikistik over sendromlu (PCOS) kadınlarda insülin direnci olanlarda myoinositol tedavisinin (günde 4 g myoinositol + 400 mcg folik asit) metformin (ortalama 1700 mg/gün) ile karşılaştırılması ve bu iki tedavinin kombinasyonunun etkinliğinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Üreme çağındaki 68 insülin direnci olan PCOS hastasının 3 aylık hasta kayıtları incelenmiştir. Oral glikoz tolerans testleri (OGTT) (75 gr) 0 ve 120 dakikada glikoz düzeylerini, prolaktin, tiroid uyarıcı hormon, yüksek yoğunluklu lipoprotein, düşük yoğunluklu lipoprotein, trigliserid, total kolesterol, folikül stimüle edici hormon, luteinizan hormon, total testosteron, serbest testosteron, dehidroepiandrosteron sülfat (DHEA-S) düzeylerini ölçülmüş ve tedavinin ardından 3 ay sonra değerlerle karşılaştırılmıştır.

PRECIS: This study examines the efficacy of myoinositol, metformin, and their combination in treating polycystic ovary syndrome among patients with insulin resistance. It reveals that all three treatments demonstrate similar short-term effects on parameters such as oral glucose tolerance, lipid profile, body mass index, and hirsutism. Notably, improvements in clinical and metabolic outcomes were observed across all treatment groups, suggesting myoinositol's comparable effectiveness to metformin without additional benefits from combination therapy.

Address for Correspondence/Yazışma Adresi: Ceyda Karadağ, MD,
Antalya City Hospital, Clinic of Gynecologic Oncology, Antalya, Turkey
Phone: +90 534 594 22 64 **E-mail:** drceydakaradag@gmail.com **ORCID ID:** orcid.org/0000-0002-9557-0932

Received/Geliş Tarihi: 22.03.2024 **Accepted/Kabul Tarihi:** 07.05.2024

Bulgular: Tüm gruplarda adet düzeni, vücut kitle indeksi (VKİ), modifiye Ferriman Gallwey skorları, OGTT'nin 0. ve 120. dakikadaki glikoz düzeyleri, total testosteron, serbest testosteron, DHEA-S düzeylerinde istatistiksel olarak anlamlı bir iyileşme gözlenmiştir (p<0,005).

Sonuç: VKİ, modifiye Ferriman Gallwey skorları ve azalan androjen düzeyleri açısından üç grup arasında fark bulunmamıştır. Myoinositolün metformin ile kombinasyonu, metformin veya yalnızca myoinositol kadar fayda sağlamamıştır.

Anahtar Kelimeler: Hirsutizm, insülin direnci, metformin, myoinositol, polikistik over sendromu

Introduction

Polycystic ovary syndrome (PCOS) is an endocrine disorder impacting around 6-14% of women in their reproductive years, with its exact cause remaining unidentified[1,2]. It is characterized by oligomenorrhea, symptoms of hyperandrogenism, and the presence of polycystic ovaries on ultrasonography[3]. Although its pathophysiology remains unclear, it is believed to be multifactorial, involving genetic factors, insulin resistance, hyperinsulinemia, and various endocrinological abnormalities[4]. Insulin resistance and the consequent hyperinsulinemia are pivotal factors in the pathophysiology of PCOS[5]. Insulin stimulates androgen production from the ovaries, with its effects manifesting directly in the ovary and indirectly in the pituitary gland[5].

The goal of treatment in patients with PCOS who do not desire gestation is to correct the symptoms of androgen excess and regulate menstrual cycles. Oral contraceptives (OCs) are the preferred choice of medication because of their efficacy in treating hirsutism and acne, as well as their protective effect against estrogen-induced effects on the endometrium. Nevertheless, OCs may exert adverse effects on insulin resistance, glucose tolerance, vascular reactivity, and coagulability[6].

Insulin-sensitizing agents are commonly used in PCOS treatment, especially in cases of insulin resistance and hyperinsulinemia. Metformin, a well-studied biguanide derivative antidiabetic, reduces gastrointestinal glucose absorption, inhibits gluconeogenesis, and enhances peripheral insulin sensitivity[7]. Myoinositol, a stereoisomer of carbon-6 sugar alcohol and member of the vitamin B group, serves as an intracellular secondary messenger in lipid synthesis, cell membrane structure, and cell growth, thereby influencing cell morphogenesis and cytogenesis[8,9]. Studies have shown that myoinositol activates enzymes that regulate glucose metabolism, and its deficiency has been linked to insulin resistance in patients with PCOS[10]. Myoinositol therapy has been shown to increase ovulation and decrease testosterone and insulin levels in PCOS patients with insulin resistance[11].

This study aimed to compare the effects of myoinositol, metformin, and their combination on clinical and laboratory parameters in patients with PCOS and insulin resistance.

Materials and Methods

The study included 68 patients aged 16-40 years who were admitted to the Akdeniz University Faculty of Medicine, Gynecology and Obstetrics Outpatient Clinic between January 2016 and August 2017 with hirsutism and/or menstrual irregularities, diagnosed with PCOS according to the European Society of Human Reproduction and Embryology (ESHRE)/ Rotterdam 2003 diagnostic criteria, and had concurrent impaired fasting glucose or impaired glucose tolerance. Before the start of the study, written approval was obtained from the Local Ethics Committee of the Faculty of Medicine of Akdeniz University (approval number: 618 - 2012-KAEK-20; date: 01.11.2017).

PCOS diagnosis was established in individuals who met two of the three criteria outlined in the ESHRE diagnostic criteria.

1. Oligomenorrhea and/or anovulation
2. Clinical and/or biochemical hyperandrogenemia findings
3. Detection of polycystic ovaries using pelvic and/or vaginal ultrasonography.

Exclusion criteria included a history of medication use for PCOS in the previous 6 months, pregnancy, diabetes, hypertension, liver or kidney diseases, systemic diseases such as heart disease for those receiving corticosteroids, use of medications affecting insulin resistance, ongoing infections, and severe insulin resistance or heart valve disease.

Participants underwent a 75-g oral glucose tolerance test (OGTT) at baseline and at the third month of treatment, following a three-day 150-200 g/day carbohydrate diet and a 12-h fasting period post-normal daily activity. Diagnostic criteria for diabetes mellitus (DM), impaired glucose tolerance, and impaired fasting glucose were based on the American Diabetes Association 2011 guidelines[12], defining the following:

- Impaired fasting glucose: fasting plasma glucose levels of 100-125 mg/dL
- Impaired glucose tolerance: 2nd hour plasma glucose levels in OGTT of 140-199 mg/dL
- DM: fasting plasma glucose levels ≥126 mg/dL or 120th minute blood sugar levels ≥200 mg/dL during OGTT.

Patients were divided into three groups according to the treatment protocols they received.

Patients were allocated into three treatment groups: Group 1 (n=22): Metformin monotherapy (oral administration of 850 mg metformin twice daily for 3 months). Group 2 (n=28): Myoinositol monotherapy (oral administration of 2 g myoinositol twice daily for 3 months). Group 3 (n=18): Combination therapy with myoinositol and metformin (oral administration of 850 mg metformin twice daily and 2 mg myoinositol twice daily for 3 months).

Metformin administration started at a dosage of 850 mg tablets, with dose titration from the first day of treatment to minimize side effects, gradually increasing to 1700 mg daily after 2 weeks.

Patients were provided detailed information regarding potential side effects associated with metformin.

Data collection included measurements of height and body weight at baseline and 3 months after treatment. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height (m). Hirsutism scores were determined and recorded using the modified Ferriman-Gallwey scoring method at initial patient assessment and at the 3-month follow-up. Hair density was assessed on a scale from 0 to 4 in nine different regions using this method: The upper lip, chin, chest area, back, waist, lower and upper abdomen, and upper arms and legs. Those with a modified Ferriman-Gallwey score of 8 were diagnosed with hirsutism. Pelvics or transvaginal ultrasonography was performed using a Toshiba-Applio 500 ultrasound device at the Akdeniz University Faculty of Medicine Obstetrics and Gynecology outpatient clinic. Polycystic ovary changes were defined as the presence of 12 or more follicles with a diameter of 2-9 mm and/or increased ovarian volume (>10 mL) on ultrasonographic examination. Clinical parameters [ovulation presence and hirsutism (Ferriman-Gallwey) scores] and biochemical parameters (75 g OGTT, high-density lipoprotein, low-density lipoprotein, triglyceride, free and total testosterone, DHEA-S) were retrospectively compared with pretreatment values after 3 months of treatment.

Statistical Analysis

Data were analyzed using the SPSS Statistics 20 statistical package. The Shapiro-Wilk test was used to determine whether the data were normally distributed. Nonparametric data are presented as median minimum-maximum, while parametric data are presented as mean ± standard deviation. In independent samples, one-way analysis of variance was used to compare normal distributed groups, and the Kruskal-Wallis test was used to compare non-normally distributed groups. Intra-group comparisons were conducted using paired samples t-tests for normally distributed data and Wilcoxon tests for non-normally distributed data. Post-hoc analysis was performed using Bonferroni correction. A significance level of $p<0.05$ was considered statistically significant.

Results

Pre-treatment demographic, clinical, and laboratory parameters were similar across all groups (Table 1). Table 2 presents the clinical and laboratory parameters of the groups after 3 months of treatment. No significant differences were observed between the groups in terms of BMI, menstrual regularity, or laboratory parameters after 3 months of treatment ($p>0.05$). The modified Ferriman-Gallwey scores of the patients after treatment were 8.64±3.82 in Group 1, 8.11±3.85 in Group 2 and 8.67±5.68 in Group 3. Hirsutism scores of 8 or higher were observed in 14 (63.6%) patients in Group 1, 14 (50%) patients in Group 2, and 8 (44.4%) patients in Group 3 after treatment.

In Group 1, significant differences were noted between pre-treatment and post-treatment values for BMI, menstrual regularity, hirsutism scores, 0-min and 120-min OGTT values, triglycerides, total cholesterol, free testosterone, total testosterone, and DHEA-S ($p<0.016$). Similar significant differences were observed in Group 2 and Group 3 between pre-treatment and post-treatment values for the aforementioned parameters ($p<0.016$). Intra-group changes and statistical comparisons of groups before and after treatment are summarized in Table 3.

There was no significant difference between the groups in terms of the incidence of impaired glucose tolerance or impaired fasting glucose after treatment ($p=0.378$). Improvements in OGTT values were observed in all groups regardless of the type of medication used. Additionally, no significant difference was found in the improvement of hirsutism scores among the three treatment groups ($p=0.265$). Similarly, there was no significant difference in menstrual cycle improvement or total weight loss between the three treatment groups ($p=0.057$, $p=0.356$, respectively).

Discussion

This study revealed no significant differences in the short-term effects of metformin, myoinositol, and their combination on OGTT, lipid profile, BMI, and hirsutism in patients with PCOS and insulin resistance. Positive changes in clinical and laboratory outcomes were observed in all three treatment groups before and after the intervention. Few studies have directly compared the effects of myoinositol, metformin, and combination therapy on clinical and metabolic parameters in women with PCOS and insulin resistance.

Previous research by Legro et al.[13] demonstrated that myoinositol treatment for 6 months led to improvements in menstrual cycles in 88% of patients with PCOS. Similarly, Gerli et al.[14] found that 70% of patients with PCOS achieved a normal menstrual pattern after 14 weeks of myoinositol therapy. Consistent with these findings, we observed improvements in menstrual parameters across all three treatment groups.

Studies investigating hirsutism scores with myoinositol treatment in PCOS have reported a significant decrease in Ferriman-Gallwey scores after 6 months of treatment[15-17]. Interestingly, our study found a statistically significant reduction in Ferriman-Gallwey scores in all three groups after only 3 months of treatment. This early response suggests that lifestyle changes and weight loss associated with the 3-month treatment regimen contributed to the observed improvement.

Several agents used in PCOS treatment target elevated serum androgen levels, which play a significant role in the clinical manifestations of the condition. Zacchè et al.[18] observed a significant decrease in free and total testosterone levels after 3 months of myoinositol treatment.

Similarly, metformin therapy reduces insulin and androgen levels, improve insulin sensitivity, and induce ovulation[19,20]. Our study corroborates these findings, demonstrating reductions in fasting glucose levels, OGTT values, and insulin

Table 1. Demographic, clinical and laboratory parameters of groups before treatment

		Group 1 (n=22)	Group 2 (n=28)	Group 3 (n=18)	p
Age (years)		26.9±6.07	23.1±4.4	25.6±5.86	0.054
Gravida		0 (0-3)	0 (0-3)	0 (0-2)	0.434
Parity		0 (0-2)	0 (0-2)	0 (0-1)	0.097
Abortus		0 (0-1)	0 (0-1)	0 (0-1)	0.735
Menstrual regularity	Oligomenorrhoea	20 (90.9%)	26 (92.9%)	14 (77.8%)	0.269
	Amenore	2 (9.1%)	2 (7.1%)	4 (22.2%)	
USG	Normal	4 (18.2%)	2 (7.1%)	2 (11.1%)	0.483
	PCOS	18 (81.8%)	26 (92.9%)	16 (88.9%)	
BMI (kg/m^2)		27.03±6.17	24.55±2.91	27.3±5.16	0.218
Hirsutism score		9 (3-18)	9 (2-19)	9 (3-27)	0.999
OGTT 0 minute		94.2±11.4	92.8±12.6	99.3±10.6	0.281
OGTT 120 minute		168.6±17.4	162±17.9	154.7±24.3	0.111
Triglycerides (mg/dL)		112±51.3	98.1±31.9	127.2±55.8	0.207
LDL (mg/dL)		100.7±26.1	101.7±15.9	105±17.2	0.833
HDL (mg/dL)		46.5±8.4	49.2±6.5	45.6±7.9	0.128
Total cholesterol (mg/dL)		168.3±32.5	176.8±22.8	168.6±23.8	0.398
Free testosterone (pg/mL)		2.71±0.89	2.41±1.05	2.52±0.88	0.293
Total testosterone (ng/mL)		0.6±0.17	0.52±0.18	0.54±0.21	0.421
DHEA-S (ug/dL)		287.2±123.6	255.3±80	303±141.4	0.523
FSH (mIU/mL)		6.14±1.73	6.09±1.86	5.2±1.31	0.059
LH (mIU/mL)		7.79±7.04	8.58±5.75	7.37±4.62	0.480
Estradiol (pg/mL)		62.5±46.5	55.1±23.4	77.3±53.3	0.377
Prolactin (ng/mL)		10.7±4.2	11.6±4.9	13.2±4.6	0.185
TSH (uIU/mL)		1.79±1.03	1.49±0.65	1.96±1.09	0.162

PCOS: Polycystic ovary syndrome, OGTT: Oral glucose tolerance tests, DHEA-S: Dehydroepiandrosterone sulfate, LDL: Low density lipoprotein, HDL: High density lipoprotein, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, USG: Ultrasonography, BMI: Body mass index

Table 2. Clinical and laboratory parameters of the groups after 3 months of treatment

		Group 1 (n=22)	Group 2 (n=28)	Group 3 (n=18)	p
BMI (kg/m^2)		26.03±5.71	23.77±2.58	26.4±4.14	0.100
Menstrual regularity	Oligomenorrhoea	10 (45.5%)	14 (50%)	4 (22.2%)	0.153
	Normal	12 (54.5%)	14 (50%)	14 (77.8%)	
Hirsutism score		8 (3-17)	7.5 (2-16)	8 (3-24)	0.767
OGTT 0 minute		85±12.6	83.1±12.7	82.7±9.9	0.667
OGTT 120 minute		108±24.4	106.7±28.7	107.1±17.9	0.729
Triglycerides (mg/dL)		103.8±43	94.6±28	115.7±44.8	0.289
LDL (mg/dL)		96.4±23.7	92.3±12.8	95.7±12.3	0.602
HDL (mg/dL)		47.4±7.9	53.1±9.9	46.7±6.7	0.062
Total cholesterol (mg/dL)		161±31.6	163.5±17.8	155.1±19.5	0.336

Table 2. Continued

	Group 1 (n=22)	Group 2 (n=28)	Group 3 (n=18)	p
Free testosterone (pg/mL)	2.38±0.68	2.03±0.92	2.11±0.63	0.196
Total testosterone (ng/mL)	0.47±0.07	0.41±0.11	0.45±0.13	0.101
DHEA-S (ug/dL)	248.6±71.2	228.5±63.6	236±81.4	0.679
FSH (mIU/mL)	4.71±0.94	4.08±1.03	4.49±0.86	0.097
LH (mIU/mL)	4.56±1.97	5.36±2.52	5.11±2.62	0.169
Estradiol (pg/mL)	41.5±16.2	35.7±9.15	47.1±18.8	0.118
Prolactin (ng/mL)	10.6±3.03	9.95±4.13	10.4±3.23	0.593
TSH (uIU/mL)	1.97±0.78	1.69±0.71	2±0.67	0.138

OGTT: Oral glucose tolerance tests, DHEA-S: Dehydroepiandrosterone sulfate, LDL: Low density lipoprotein, HDL: High density lipoprotein, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, BMI: Body mass index

Table 3. Intra-group changes before and after treatment

Pre-treatment		Group 1 (n=22)		p Pre-treatment	Group 2 (n=28)		p Pre-treatment	Group 3 (n=18)		p
		Post-treatment			Post-treatment			Post-treatment		
BMI		27 ±6.1	26 ±5.7	**0.002**	24.5 ±2.9	23.7 ±2.5	**0.001**	27.3 ±5.1	26.4 ±4.1	**0.002**
Menstrual regularity	Amenore	2 (%9.1)	-	**0.001**	2 (7.1%)	-	**0.001**	4 (22.2%)	-	**0.001**
	Oligomenorrhoea	20 (90.9%)	10 (45.5%)		26 (92.9%)	14 (50%)		14 (77.8%)	4 (22.2%)	
	Normal	-	12 (54.5%)		-	14 (50%)		-	14 (77.8%)	
Hirsutism score		9 (3-18)	8 (3-17)	**0.004**	9 (2-19)	7.5 (2-16)	**0.001**	9 (3-27)	8 (3-24)	**0.001**
OGTT 0 minute		94.2 ±11.4	85 ±12.6	**0.003**	92.8 ±12.6	83.1 ±12.7	**0.001**	99.3 ±10.6	82.7 ±9.9	**0.001**
OGTT 120 minute		168.6 ±17.4	108 ±24.4	**0.001**	162 ±17.9	106.7 ±28.7	**0.001**	154.7 ±24.3	107.1 ±17.9	**0.001**
Triglycerides (mg/dL)		112 ±51.3	103.8 ±43	**0.006**	98.1 ± 31.9	94.6 ±28	**0.091**	127.2 ±55.8	115.7 ±44.8	**0.003**
LDL (mg/dL)		100.7 ±26.1	96.4 ±23.7	0.038	101.7 ±15.9	92.3 ±12.8	**0.004**	105 ±17.2	95.7 ±12.3	**0.009**
HDL (mg/dL)		46.5 ±8.4	47.4 ±7.9	0.034	49.2 ±6.5	53.1 ±9.9	**0.002**	45.6 ±7.9	46.7 ±6.7	**0.193**
Total cholesterol (mg/dL)		168.3 ±32.5	161 ±31.6	**0.004**	176.8 ±22.8	163.5 ±17.8	**0.001**	168.6 ±23.8	155.1 ±19.5	**0.001**
Free testosterone (pg/mL)		2.71 ±0.89	2.38 ±0.68	**0.003**	2.41 ±1.05	2.03 ±0.92	**0.001**	2.52 ±0.88	2.11 ±0.63	**0.012**
Total testosterone (ng/mL)		0.6 ±0.17	0.47 ±0.07	**0.001**	0.52 ±0.18	0.41 ±0.11	**0.001**	0.54 ±0.21	0.45 ±0.13	**0.007**
DHEA-S (ug/dL)		287.2 ±123.6	248.6 ±71.2	**0.007**	255.3 ±80	228.5 ±63.6	**0.001**	303 ±141.4	236 ±81.4	**0.001**

OGTT: Oral glucose tolerance tests, DHEA-S: Dehydroepiandrosterone sulfate, LDL: Low density lipoprotein, HDL: High density lipoprotein, LH: Luteinizing hormone, FSH: Follicle stimulating hormone, BMI: Body mass index

resistance parameters with both metformin and myoinositol therapy.

A study by Nas and Tűű[21] comparing combined treatments of metformin, myoinositol, and their combination found no significant differences in effectiveness between the myoinositol and metformin groups. Similarly, a recent meta-analysis comparing metformin and myoinositol reported similar metabolic effects in the short term, with myoinositol being better tolerated because of fewer gastrointestinal side effects[22].

Study Limitations

The limitations of our study include its retrospective nature and the lack of a control group receiving only lifestyle recommendations. Nonetheless, our findings support the efficacy of myoinositol as a treatment for PCOS and underscore its potential advantages over metformin, particularly in terms of tolerability and side effect profile.

Conclusion

Given the uncertain etiopathogenesis of PCOS, treatment primarily focuses on symptom management. However, addressing underlying factors such as hyperandrogenemia and insulin resistance can lead to normalization of the clinical picture. Our study suggests that myoinositol therapy is at least as effective as metformin in improving clinical and laboratory parameters in patients with PCOS and insulin resistance. Furthermore, combining myoinositol with metformin did not provide any additional benefits. Considering the reported side effects associated with metformin, myoinositol has emerged as a promising treatment option for patients with insulin-resistant PCOS.

Ethics

Ethics Committee Approval: Before the start of the study, written approval was obtained from the Local Ethics Committee of the Faculty of Medicine of Akdeniz University (approval number: 618 - 2012-KAEK-20; date: 01.11.2017).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: C.K., Ö.B., Concept: C.K., Design: C.K., M.S., Data Collection or Processing: M.S., S.S., Analysis or Interpretation: Ö.B., M.S.B., Literature Search: B.K., S.S., Writing: C.K.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. Fertil Steril 2018;110:364-79.
2. Sanchón R, Gambineri A, Alpañés M, Martínez-García MÁ, Pasquali R, Escobar-Morreale HF. Prevalence of functional disorders of androgen excess in unselected premenopausal women: a study in blood donors. Hum Reprod 2012;27:1209-16.
3. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19-25.
4. Zawadzki JK, Danif A. Diagnostic criteria for polycystic ovary syndrome towards a rational approach. In: Dunaif A, Givens JR, Hasetine FP, et al, (eds). Polycystic ovary syndrome. Cambridge, England: Blackwell Science 1992;377-84.
5. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997;18:774-800.
6. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016;65:1-103.
7. Baillargeon JP, Iuorno MJ, Nestler JE. Insulin sensitizers for polycystic ovary syndrome. Clin Obstet Gynecol 2003;46:325-40.
8. Papaleo E, Unfer V, Baillargeon JP, Fusi F, Occhi F, De Santis L. Myo-inositol may improve oocyte quality in intracytoplasmic sperm injection cycles. A prospective, controlled, randomized trial. Fertil Steril 2009;91:1750-4.
9. Osborne NN, Tobin AB, Ghazi H. Role of inositol trisphosphate as a second messenger in signal transduction processes: an essay. Neurochem Res 1988;13:177-91.
10. Costantino D, Minozzi G, Minozzi E, Guaraldi C. Metabolic and hormonal effects of myo-inositol in women with polycystic ovary syndrome: a double-blind trial. Eur Rev Med Pharmacol Sci 2009;13:105-10.
11. Gayoso-Diz P, Otero-González A, Rodriguez-Alvarez MX, Gude F, García F, De Francisco A, et al. Insulin resistance (HOMA-IR) cut-off values and the metabolic syndrome in a general adult population: effect of gender and age: EPIRCE cross-sectional study. BMC Endocr Disord 2013;13:47.
12. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2011;34 (Suppl 1):S62-9.
13. Legro RS, Arslanian SA, Ehrmann DA, Hoeger KM, Murad MH, Pasquali R, et al. Diagnosis and treatment of polycystic ovary syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2013;98:4565-92.
14. Gerli S, Papaleo E, Ferrari A, Di Renzo GC. Randomized, double blind placebo-controlled trial: effects of myo-inositol on ovarian function and metabolic factors in women with PCOS. Eur Rev Med Pharmacol Sci 2007;11:347-54.
15. Somunkiran A, Yavuz T, Yucel O, Ozdemir I. Anti-Müllerian hormone levels during hormonal contraception in women with polycystic ovary syndrome. Eur J Obstet Gynecol Reprod Biol 2007;134:196-201.
16. Minozzi M, Costantino D, Guaraldi C, Unfer V. The effect of a combination therapy with myo-inositol and a combined oral contraceptive pill versus a combined oral contraceptive pill alone on metabolic, endocrine, and clinical parameters in polycystic ovary syndrome. Gynecol Endocrinol 2011;27:920-4.
17. Minozzi M, D'Andrea G, Unfer V. Treatment of hirsutism with myo-inositol: a prospective clinical study. Reprod Biomed Online 2008;17:579-82.

18. Zacchè MM, Caputo L, Filippis S, Zacchè G, Dindelli M, Ferrari A. Efficacy of myo-inositol in the treatment of cutaneous disorders in young women with polycystic ovary syndrome. Gynecol Endocrinol 2009;25:508-13.
19. Norman RJ, Kidson WJ, Cuneo RC, Zacharin MR. Metformin and intervention in polycystic ovary syndrome. Endocrine Society of Australia, the Australian Diabetes Society and the Australian Paediatric Endocrine Group. Med J Aust 2001;174:580-3.
20. Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Martikainen H, Tapanainen JS. Metformin versus ethinyl estradiol-cyproterone acetate in the treatment of nonobese women with polycystic ovary syndrome: a randomized study. J Clin Endocrinol Metab 2003;88:148-56.
21. Nas K, Tűű L. A comparative study between myo-inositol and metformin in the treatment of insulin-resistant women. Eur Rev Med Pharmacol Sci 2017;21(2 Suppl):77-82.
22. Facchinetti F, Orrù B, Grandi G, Unfer V. Short-term effects of metformin and myo-inositol in women with polycystic ovarian syndrome (PCOS): a meta-analysis of randomized clinical trials. Gynecol Endocrinol 2019;35:198-206.