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The Effect of Evening Primrose Oil on Clinical Manifestations in Women with Polycystic Ovary Syndrome: A Triple-blind, Randomized Controlled Trial

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ABSTRACT

Background & aim: Polycystic ovary syndrome (PCOS) is a common hormonal disease. This study examined the effect of evening primrose oil (EPO) on hirsutism, depression, menstrual irregularities, anthropometric indices (primary outcomes), and side effects as secondary outcomes in patients diagnosed with PCOS.

Methods: This randomized controlled trial involved 62 women aged 18–45 years with PCOS, recruited through convenience sampling in Tabriz, Iran, from November 2022 to November 2023. Participants were randomly allocated using block randomization to intervention (n=31) and control (n=31) groups. The intervention group received 1000 mg/day EPO, while controls received identical placebo capsules for three months. Before and after intervention, hirsutism (Ferriman-Gallwey score), menstrual characteristics, depression (Beck Depression Inventory), and menstrual bleeding (Higham Scale) were assessed. Anthropometric indices were also measured. Data were analyzed using SPSS 26, Fisher's exact, chi-square, chi-square trend, independent-samples t-tests, and analysis of covariance (ANCOVA).

Results: After the intervention, no significant differences were observed between groups in terms of depression (adjusted mean difference: 0.4, 95% confidence interval: 0.3 to 2.5), hirsutism (-0.5, -2.3 to 1.3), menstrual bleeding (-5.8, -18.7 to -7.1), menstrual cycle length (-3.1, -7.2 to 0.9), duration of bleeding (-3.0, -1.1 to 0.5), waist circumference (-0.2, -0.8 to 1.3), hip size (-8.1, -17.7 to 1.5), and body mass index (-0.2, -0.7 to 2.0).

Conclusion: Administration of EPO has no significant effect on clinical symptoms in women with PCOS. Nevertheless, additional research is advised to reach a definitive conclusion in this field.

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Introduction

Polycystic ovary syndrome (PCOS) is a multifaceted condition comprising various disorders affecting the metabolism, endocrine system, and reproduction. The global prevalence of this condition is estimated to be between 5 and 12% of women, while in Iran, it affects between 7.1 and 14.6% of women. Its prevalence among reproductive-age individuals could reach 12-21% of the female population (1-2). PCOS is characterized by a multifaceted etiology, which

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suggests that metabolic dysfunctions and reproductive irregularities interact. Two contributing factors to its development are hyperandrogenism and insulin resistance. Only a limited percentage of PCOS cases can be attributed to genetic predispositions. Its etiology is mainly attributed to environmental factors derived from perinatal conditions influenced by lifestyle decisions (3).

PCOS has a significant effect on women's health. Patients with PCOS are more susceptible to reproductive issues such as infertility, ovarian disorders, and endometrial cancer. Common outcomes include sadness, constant anxiety, and losing faith in oneself. Additionally, PCOS is associated with several metabolic conditions, such as hypertension, dyslipidemia including high cholesterol, insulin resistance and type 2 diabetes mellitus (DM) (4-5).

Diverse strategies are advised for the management of PCOS, encompassing lifestyle adjustments, dietary alterations, and varying levels of physical activity. These techniques may also involve surgical and pharmaceutical procedures. Insulin sensitizers and hormonal controls are known for their effectiveness in minimizing the symptoms of PCOS, particularly in the treatment of hirsutism. The medications commonly used for PCOS include clomiphene citrate, metformin, letrozole, spironolactone, and tamoxifen (6-10). It is considered necessary to continue scientific inquiry into safer therapeutic agents, particularly considering the potential disturbances to glucose metabolism, vascular function, and hemostasis (11-12).

Modern research is particularly focused on herbal medicines with relatively minimal side effects, which is an important factor for women in their reproductive years. Nevertheless, despite being natural products with therapeutic characteristics, herbal drugs can also have harmful consequences due to their many bioactive components. Research on various herbal plants has shown encouraging findings regarding fertility indices. These include significant reductions in levels of luteinizing hormone (LH), testosterone, and estradiol; increased levels of follicle-stimulating hormone (FSH); oocyte maturation; and beneficial effects on blood glucose concentration, insulin levels, lipid profile, and endometrial tissue parameters (13-16).

Due to its medicinal properties, evening primrose oil (EPO) has garnered attention. Its efficacy has been mentioned in conditions such as atopic eczema (17-18), schizophrenia (19), and rheumatologic diseases (20). Animal studies have demonstrated that EPO significantly affects serum levels of LH, FSH, testosterone, glucose, and insulin (21). The components of EPO, which contain significant amounts of polyunsaturated fats, particularly the essential varieties known as omega-3 and omega-6 (22), may modulate inflammatory pathways in patients with PCOS, thereby reducing hirsutism and insulin resistance (23). Several studies indicate that omega-3 fatty acids may help resolve metabolic issues and improve serum adiponectin concentration, insulin sensitivity, and lipid profile in PCOS patients (24). Aftan et al. found that EPO and soybean oil supplements may minimize clinical symptoms of PCOS (25). Atteia et al. found that EPO may treat obesity-related hormonal abnormalities and menstrual irregularities in obese female mice (22). Mert et al. examined the effect of EPO (Oenothera biennis) on levels of adiponectin and specific metabolic markers within a fructose-based experimental syndrome model in rats. According to their findings, EPO has antioxidant qualities that reduce oxidative stress and increase levels of adiponectin and insulin sensitivity. It also has anti-inflammatory properties and can regulate dyslipidemia and systolic blood pressure, which helps prevent atherosclerosis (26).

The prevalence of PCOS among Iranian women ranges from 4.41% to 19.5% (27). The current pharmacological therapies for PCOS are costly and have side effects. Additionally, there is a lack of human research comparing the benefits of EPO on the clinical symptoms of PCOS. This study examined the effect of EPO on hirsutism, depression, menstrual irregularities, anthropometric indices (primary outcomes), and side effects as secondary outcome in patients diagnosed with PCOS.

Materials and Methods

This study was a triple-blind, randomized, controlled experiment in which participants, researchers, and data analysts were blinded to

the intervention they received. This study was registered at the Iranian Registry of Clinical Trials (Code: IRCT20120718010324N73—date of registration: 08/11/2022; URL: https://irct.behdasht.gov.ir/user/trial/64287/view; Date of first registration: 21/11/2022.

The study included women aged 18 to 45 who had been diagnosed with PCOS and met the inclusion criteria. The study was conducted in Tabriz, Iran, at two women's hospitals, the two endocrine clinic and private facilities. Sampling began in November 2022 and continued until November 2023.

Participants qualified if they met these criteria: confirmed diagnosis of PCOS based on the Androgen Excess Society criteria in 2006, which included hirsutism, acne, androgenic alopecia, and/or biochemical hyperandrogenemia, accompanied by oligo-anovulation and/or polycystic ovaries (28). In addition, the following were prerequisites for participation: literacy proficiency, a body mass index (BMI) in the 18.5–40 range, age between 18 and 45 years, abstinence from vitamin, mineral, and omega-6 supplementation for 3 months before the study, absence of androgen-producing tumors, enlarged adrenal glands, Cushing's disease, thyroid disorders, pregnancy or lactation, ongoing infertility treatment, prior ovarian surgery, dietary supplement use, alcohol consumption, and smoking. The exclusion criteria encompassed the occurrence of any unexpected or unforeseen event during the trial that could interfere with the study outcomes or participant safety, including acute illness, hospitalization, surgery, trauma, severe infection, or other major medical events

Based on the variables of hirsutism and depression as determined by the G-Power software, 62 individuals comprised the sample for this study. According to the results of study by Alspach (2021) concerning the variable of hirsutism, a sample size of two individuals was determined under the assumptions that $M_1 = 9.1$, $M_2 = 6.37$ (with a 30% increase as a consequence of the treatment), $SD_1 = SD_2 = 0.3$, two-sided $\alpha = 0.05$, and Power = 95% (29). Based on Mirghafourvand et al. study (2018) [30] on depression, a sample size of 28 persons was computed using the following assumptions: $M_1 = 27.4$, $M_2 = 19.18$ (with a 30% reduction by intervention effect), SD1= SD2= 10.5, $\alpha = 0.05$ (two-sided), and Power = 80% (30). Given a 10% dropout rate and the larger sample size determined by the depression variable, a final sample size of 31 people per group was considered.

Sampling was initiated at the centers after obtaining the necessary approvals and registrations, including approval from the Ethics Committee of Tabriz University of Medical Sciences

After identifying women with PCOS through convenience sampling method, the researcher screened them for inclusion or exclusion criteria. Selected individuals were informed of all necessary information regarding the research procedures. Then, informed written consent was secured from all participants who expressed a desire to participate in the study. Each participant completed a questionnaire on demographic characteristics, menstrual cycle characteristics, and the Beck Depression Inventory. The researcher also measured individuals' physical measurements including waist and hip girth alongside BMI were documented using the designated forms.

Participants were assigned to one of two categories according to whether they had received therapy: intervention and control. Random allocation was carried out using block sizes comprising four and six units to evenly allocate participants to the intervention and control groups while maintaining a 1:1 ratio. For allocation concealment, opaque envelopes were numbered sequentially from 1 to 62. An individual not involved in the research performed the allocation sequence and concealment.

Participants were given 90 capsules of EPO or a placebo provided by Tasnim Pharmaceuticals Company. Each EPO capsule contained 1000 mg of pure evening primrose oil extracted from Oenothera biennis seeds using cold-press methods and encapsulated in soft gelatin capsules. Although the exact fatty acid percentages were not specified on the manufacturer's product leaflet, evening primrose oil typically contains approximately 7–10% gamma-linolenic acid (GLA) and 65–80% linoleic acid (31). Each placebo capsule contained 1000

mg of inert sunflower oil, in an identical soft gelatin shell, making it indistinguishable from the EPO capsules in shape, size, color, and odor. Each participant received a set of opaque glass containers with identical designs, indistinguishable in color and shape, and sequentially numbered for personal dispensing. Initially, each participant received a glass container containing 30 capsules, each with a dose of 1000 milligrams, for one month. A new container for the following month was distributed at the end of each month, resulting in a three-month treatment period. The intervention group received one EPO capsule daily, while the other group received a placebo. Consuming EPO capsules and placebos involved taking one capsule daily with a glass of water during main meals. Participants were followed up monthly during capsule distribution for adherence and adverse events, and study outcomes were assessed at baseline and at the end of the 3-month intervention period.

The instruments for data collection included a questionnaire on demographic characteristics, a menstrual cycle assessment tool, an anthropometric indices checklist, the Ferriman-Gallwey score for assessing hirsutism, the Beck Depression Inventory, the Higham chart, a side-effect tracking form, and a record sheet used to track drug administration.

The socio-demographic characteristics questionnaire includes questions regarding age, marital status, occupation, and monthly income, education level of the individual and her spouse, residency status, number of pregnancies, births, living children, abortions, and history of infertility. It was administered through interviews with the individual at the beginning of the study and completed accordingly.

The menstrual cycle assessment instrument gathered data regarding typical cycle length and bleeding duration over the preceding three months. Participants filled it out both at baseline and again three months following the treatment period. The amount of menstrual bleeding was determined using the Higham chart, a visual tool for assessing menstrual blood loss. In this chart, a menstrual pad with small blood stains is scored as 1, half of the pad soaked with blood is scored as 5, and a complete soaking with blood is scored as 20. Additionally, clots are scored between 1 and 5 based on their size. In this two-dimensional chart, the horizontal rows represent the days of menstruation, and the vertical columns represent the pads soaked with blood after each change. The degree of blood soaking is marked within the chart for each day of menstruation, indicating mild, moderate, or severe bleeding. At the end of menstruation, each mark is multiplied by its corresponding score, and the resulting numbers are added together to calculate the total score. A score below 50 indicates mild bleeding, 51 to 100 indicates moderate bleeding, and above 100 indicates severe bleeding during menstruation. This chart also records the duration of bleeding (32). The psychometric properties of this instrument have been validated within the Iranian population (33).

Anthropometric indices checklist contained fields for the examiner to record height, weight, and the circumferences of the waist and hips. Subsequently, the standard quotient of weight over height squared (in metric units) was applied to compute the BMI.

All hirsutism evaluations were conducted by the first author, who was blinded to participants' group assignments. Before the trial began, the assessor completed practical training on the Ferriman–Gallwey scoring system under the supervision of a gynecologist, who directly verified her scoring consistency on initial patient examinations prior to formal data collection. The Ferriman-Gallwey score was used to assess hirsutism twice: once before the intervention (pre-test) and once three months after the intervention (post-test). This scoring system assesses hair growth in nine body areas and is graded on a Likert scale from 0 to 4. A score of 0 indicates no hair growth, while a score of 4 indicates excessive hair growth. The maximum score on this questionnaire is 36, with a minimum of 0 (34). The psychometric properties of this instrument have been validated within the Iranian population (35).

This study used the 21-item Beck Depression Inventory to measure depression in participants. The test was first created in 1961 and later updated in 1996 to include more symptoms and match Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. It is a self-report questionnaire that takes about 5 to 10 minutes to complete. It has 21 items, each scored

from 0 to 3, covering symptoms like sadness, guilt, sleep problems, loss of appetite, and low self-esteem. A reading level of around fifth or sixth grade is needed to understand the questions. Total scores range from 0 to 63, with higher scores meaning more severe depression: 0–13 (minimal), 14–19 (mild), 20–28 (moderate), and 29–63 (severe). The Persian version was tested by Ghasemzadeh et al., who found good reliability, with a Cronbach's alpha of 0.87 and a reliability coefficient of 0.73 (36).

Throughout the trial, all untoward clinical occurrences and their intensity were documented using side-effect tracking form.Each participant's daily EPO or placebo consumption was written on medication usage checklist..

Statistical analyses were carried out using IBM SPSS Statistics, version 26. Baseline comparisons between the two study arms with respect to demographic and obstetrics variables were performed utilizing Fisher's exact test, chi-square analysis, chi-square test for linear trend, and independent-samples t-test, as appropriate. To evaluate the effect of the intervention, pre-treatment group differences were assessed via independent t-test. Post-intervention comparisons were made using analysis of covariance (ANCOVA), adjusting for baseline values, stratification indicators, and other relevant covariates. All efficacy evaluations adhered to the intention-to-treat principle, with statistical significance set at a two-sided alpha level of 0.05.

Results

A total of 241 individuals were assessed, of whom 155 were ineligible for the study. Also, 24 individuals met the inclusion criteria but withdrew from the study due to their lack of consent. Consequently, 62 women aged 18 to 45 with PCOS, all meeting the inclusion criteria, entered the study after providing informed consent. They were randomly split into intervention and control arms and received medication or placebo for 12 weeks, depending on their group. During the first month of follow-up, one person withdrew from the study due to skin rashes, and one person due to fear of medication. In the second month of follow-up, one person withdrew due to obesity and two due to unwillingness to continue medication and stomach pain. In the third month, no one from either group withdrew from the study. After 12 weeks, 62 individuals were reassessed, and the data were analyzed following the intervention. All participants, regardless of protocol adherence or treatment received, were analyzed according to their original assigned group (ITT= Intention-to-treat) (Figure 1).

A mean age of 28.8 years (SD: 7.9) was noted for the EPO-assigned participants, compared to 34.7 years (SD: 7.8) for the placebo-assigned participants (P = 0.005). The average (SD) duration of PCOS in the EPO group was 7.6 years (6.5), and in the placebo group, it was 12.35 years (6.4), which was significantly different (P = 0.003). The majority of participants across both study arms were married (58.1% in the EPO group, 77.4% in the placebo group), with a statistically significant difference between the two groups (P = 0.016). Regarding monthly income sufficiency, 61.3% in the EPO group and 71.0% in the placebo group reported sufficient income to cover living expenses, with a significant difference (P = 0.041). The cause of infertility was PCOS in 85.7% of women in the EPO group and 80.0% in the placebo group, which did not indicate a significant difference (P >0.99) (Table 1 & 2).

Table 1. Comparison of sociodemographic characteristics between the intervention and control groups

Variable	Evening primrose oil (N=31)	Placebo (N=31)	P-Value
	Mean (SD*)	Mean (SD*)	
Age (Year)	28.8 (7.9)	34.7 (7.8)	†0.005
Variable	**Frequency (%)**	**Frequency (%)**	**P-Value**
Education			‡0.001
Primary school	0 (0)	2 (6.5)	
Secondary school	1 (3.2)	3 (9.7)	
High school	2 (6.5)	5 (16.1)	
Diploma	6 (19.4)	14 (45.2)	
University	22 (71.0)	7 (22.6)	

Variable	Evening primrose oil (N=31)	Placebo (N=31)	P-Value
	Mean (SD*)	Mean (SD*)	
Husband Education			‡0.060
Primary school	0 (0)	1 (4.3)	
Secondary school	2 (10.5)	4 (17.4)	
High school	0 (0)	3 (13.0)	
Diploma	5 (26.3)	7 (30.4)	
University	12 (63.2)	8 (34.8)	
Job			§0.362
Housewife	16 (59.3)	22 (78.6)	
Work at home	2 (7.4)	1 (3.6)	
Employed	9 (33.3)	5 (17.9)	
Marriage status			§0.016
Married	18 (58.1)	24 (77.4)	
Single	13 (41.9)	4 (12.9)	
Widow	0 (0)	2 (6.5)	
Divorced	0 (0)	1 (3.2)	
Sufficient monthly income for living expenses			‡0.041
Completely enough	11 (35.5)	5 (16.1)	
Quite enough	19 (61.3)	22 (71.0)	
Not enough at all	1 (3.2)	4 (12.9)	
Inhabitancy			§0.127
Personal	24 (77.4)	26 (83.9)	
Rental	3 (9.7)	5 (16.1)	
The type of oil used in cooking			0.008§
Liquid oil	19 (67.9)	9 (29.0)	
Solid oil	1 (3.6)	4 (12.9)	
Other	8 (28.6)	18 (58.1)	
Fish consumption per month			§0.631
No	10 (33.3)	15 (48.4)	
Once	8 (26.7)	5 (16.1)	
Twice	2 (6.7)	2 (6.5)	
Thrice	10 (33.3)	9 (29.0)	
Fish consumption per week			§0.155
No	15 (50.0)	19 (61.3)	
Once	13 (43.3)	7 (22.6)	
Twice	0 (0)	3 (9.7)	
Thrice	2 (6.7)	2 (6.5)	

*Standard Deviation; †Independent t test; ‡ Chi-square trend; § Fisher's exact test; ¥ Polycystic ovary syndrome

Post-intervention depression scores were found to be 8.9 (SD: 5.6) in the EPO-assigned participants, compared with 8.6 (SD: 6.0) in the placebo-assigned participants. Based on the ANCOVA test and controlling for variables such as pre-intervention depression score, stratification factor, age, duration of illness, income, and education, the between-group difference did not reach statistical significance, with an adjusted mean difference of 0.4 (95% CI: -3.3 to 2.5, P = 0.801).

At the post-intervention assessment, the EPO group exhibited a mean hirsutism score of 10.6 (SD: 4.8), whereas the placebo group had a mean of 13.9 (SD: 5.1). Based on the ANCOVA test, controlling for variables such as pre-intervention hirsutism score, stratification factor, age, duration of illness, income, and education, group difference was non-significant (AMD: -5.0; 95% CI: -2.3 to 1.3; P = 0.587). After the intervention, the mean (SD) Higham score in the EPO group was 51.6 (22.7), and in the placebo group, it was 80.4 (50.5). Based on the ANCOVA test, controlling for variables such as pre-intervention Higham score, stratification factor, age, duration of illness, income, and education, there was no statistically significant difference between the two groups (AMD: -5.8; 95% CI: -18.7 to 7.1; P = 0.370).

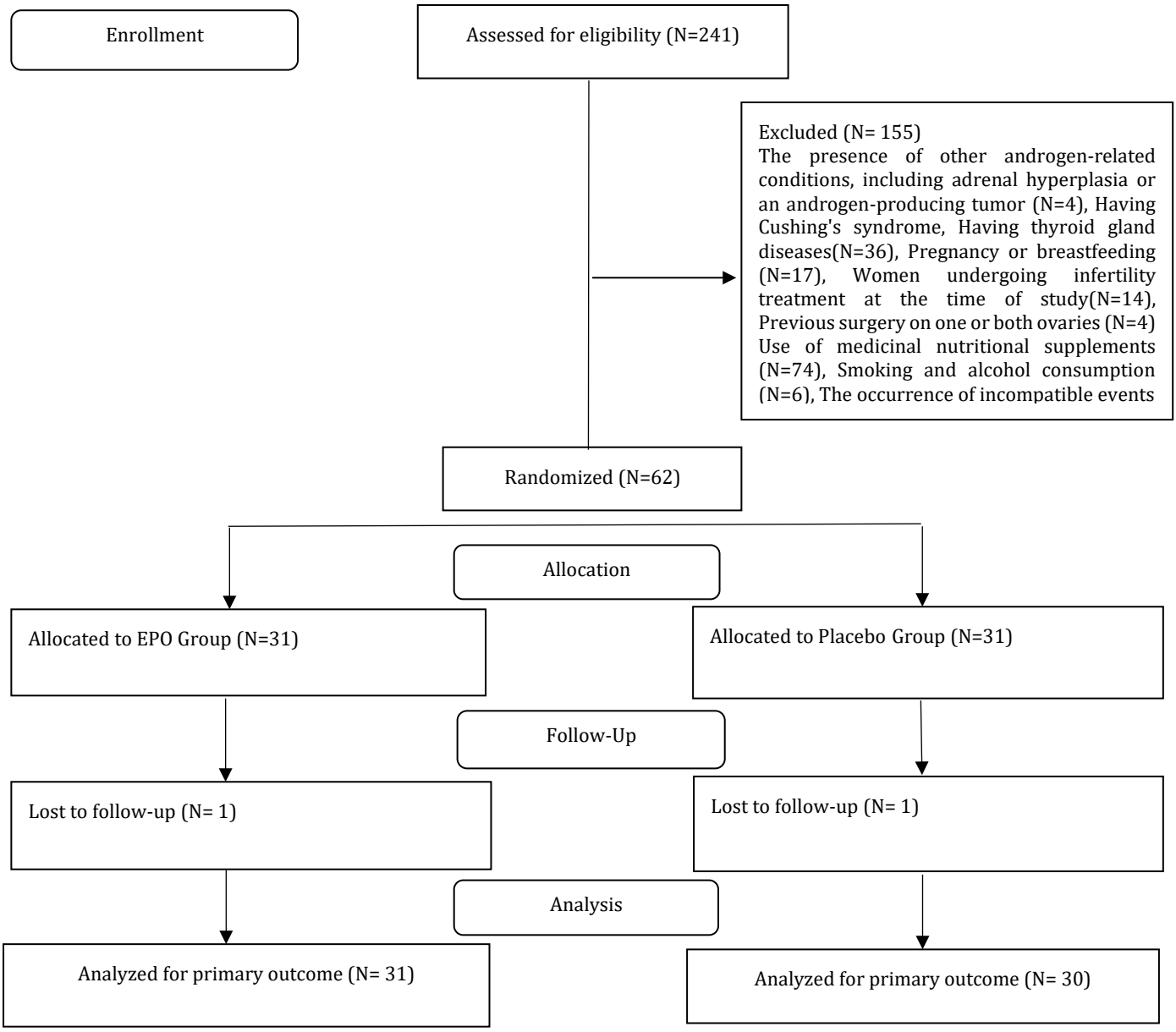


Figure 1. CONSORT Flowchart of the study

Post-treatment mean bleeding duration was 6.0 days (SD: 1.5) in the EPO group and 6.9 days (SD: 1.7) in the placebo group. Based on the ANCOVA test, controlling for variables such as baseline values, stratification factor, age, duration of illness, income, and education, no significant group difference was found (AMD: -3.0; 95% CI: -1.1 to 0.5; P = 0.408).

Post-treatment mean intermenstrual interval was 33.2 days (SD: 13.5) in the EPO group and 35.3 days (SD: 11.5) in the placebo group. According to the ANCOVA test, controlling for baseline values, stratification factor, age, duration of illness, income, and education, no significant group difference was found (AMD: -3.1; 95% CI: -7.2 to 0.9; P = 0.129).

Table 2. Comparison of infertility, PCOS, and obstetric characteristics between the intervention and control groups

Variable	Evening primrose oil (N=31)	Placebo (N=31)	P-Value
	Mean (SD*)	Mean (SD*)	
Years of infertility (Year)	7.1 (5.7)	5.3 (2.6)	0.490†
Duration of PCOS (Year)	7.6 (5.6)	12.4 (6.4)	0.003†
Variable	**Frequency (Percent)**	**Frequency (Percent)**	
Infertility			0.333‡
Yes	7 (35.0)	6 (22.2)	
No	13 (65.0)	21 (77.8)	
Cause of infertility			§1.000
PCOS¥	6 (85.7)	4 (80.0)	
Other	1 (14.3)	1 (20.0)	
Number of births			§0.453
1	6 (50.0)	6 (50.0)	
2	5 (41.7)	10 (38.5)	
3	1 (8.3)	7 (26.9)	
Number of pregnancies			§0.191
0	1 (8.3)	0 (0)	
1	6 (50.0)	7 (26.9)	
2	2 (16.7)	10 (38.5)	
3	3 (25.0)	9 (34.6)	
Living child			§0.170
0	1 (8.3)	0 (0)	
1	7 (58.3)	9 (34.6)	
2	3 (25.0)	10 (38.5)	
3	1 (8.3)	7 (26.9)	
Abortion			‡0.658
No	6 (50.0)	15 (57.7)	
Yes	6 (50.0)	11 (42.3)	

*Standard Deviation; †Independent t test; ‡ Chi-square trend; § Fisher's exact test; ¥ Polycystic ovary syndrome

Post-treatment mean BMI was 26.2 (SD: 4.4) in the EPO group and 28.5 (SD: 4.4) in the placebo group. According to the ANCOVA test, controlling for baseline BMI, stratification factor, age, duration of illness, income, and education, no significant group difference was found (AMD: -2.0; 95% CI: -7.0 to 2.0; P = 0.231).

Post-treatment mean waist circumference was 87.1 cm (SD: 8.3) in the EPO group and 93.7 cm (SD: 19.7) in the placebo group. As per ANCOVA, controlling for baseline values, stratification factor, age, duration of illness, income, and education, group difference was non-significant (AMD: -2.0; 95% CI: -8.0 to 1.3; P = 0.638).

Following the treatment period, the mean (SD) hip circumference in the EPO group was 105.0 (10.3), and in the placebo group, it was 111.9 (20.0). As per ANCOVA and controlling for baseline values, stratification factor, age, duration of illness, income, and education, group difference was non-significant (AMD: -8.1; 95% CI: -17.7 to 1.2; P = 0.095) (Table 3).

In terms of side effects, in the EPO group, one participant discontinued medication due to skin rashes and one due to weight gain. In the placebo group, two cases of discontinuation due to abdominal pain and fear of medication were observed.

Table 3. Comparison of clinical manifestations between the intervention and control groups at baseline and after the intervention

Variable	Evening primrose oil (N=31) Mean (standard deviation)	Placebo (N=31) Mean (standard deviation)	Mean difference (95% confidence interval)	P-Value
Depression				
Before intervention	15.0 (7.8)	11.4 (7.0)	3.6 (-1.2 to 7.3)	0.062*
After the intervention	8.9 (5.6)	8.6 (6.0)	0.4 (-3.3 to 2.5)	0.801†
Hirsutism				
Before intervention	12.0 (5.8)	14.3 (5.4)	-2.4 (-5.2 to 0.5)	0.099*
After the intervention	10.6 (4.8)	13.9 (5.1)	-0.5 (-2.3 to 1.3)	0.587†
Higham's score				
Before intervention	67.7 (38.0)	92.3 (68.2)	-24.7 (-53.1 to 3.7)	0.087*
After the intervention	51.6 (22.7)	80.4 (50.5)	-5.8 (-18.7 to 7.1)	0.370†
Duration of bleeding				
Before intervention	6.4 (1.6)	7.0 (2.0)	-0.6 (-1.5 to 0.3)	0.199*
After the intervention	6.0 (1.5)	6.9 (71)	-0.3 (-1.1 to 0.5)	0.408†
The time interval between menstrual cycles				
Before intervention	38.0 (16.4)	36.1 (12.2)	1.9 (-5.5 to 9.4)	0.605*
After the intervention	33.2 (13.5)	35.3 (11.5)	-3.1 (-7.2 to 0.9)	0.129†
Body Mass Index				
Before intervention	26.3 (4.4)	28.4 (4.3)	-2.1 (-4.3 to 0.1)	0.062*
After the intervention	26.2 (4.4)	28.5 (4.4)	-0.2 (-0.7 to 0.2)	0.231†
Waist circumference				
Before intervention	86.6 (8.8)	93.6 (19.3)	-7.0 (-14.6 to 0.6)	0.070*
After the intervention	87.1 (8.3)	93.7 (19.7)	0.2 (-0.8 to 1.3)	0.638†
Hip circumference				
Before intervention	104.4 (9.8)	108.0 (12.6)	-3.7 (-9.4 to 2.1)	0.205*
After the intervention	105.0 (10.3)	111.9 (20.0)	-8.1 (-17.7 to 1.5)	0.095†

* Independent t-test; † ANCOVA with controlling for baseline values, stratification factor, age, duration of illness, income, and education

Discussion

The present triple-blind, randomized controlled trial aimed to evaluate the effects of evening primrose oil (EPO; 1000 mg/day for three months) on depression, hirsutism, menstrual irregularities, anthropometric indices, and adverse events in women with PCOS. The results showed that EPO did not significantly affect these clinical symptoms— including depression, hirsutism, menstrual bleeding volume, intermenstrual intervals, duration of bleeding, and anthropometric indices— compared with placebo.

This study found no group difference in mean depression scores after the intervention. EPO is mainly a potential treatment for depression and mood disorders in women. However, its effect on the treatment of depression and mood disorders in women remains controversial, as there are different perspectives on its effectiveness in treating these problems (37). For example, a study by Horrobin (1983) showed that EPO is an excellent adjunctive agent in treating premenstrual syndrome (PMS) symptoms such as irritability, depression, and water retention (38). However, Callender et al. (1988) detected no significant difference in effectiveness between active EPO and placebo (39). Momeni et al. (2013), in their clinical trial comparing vitex agnus-castus oil with EPO for depression in women, reported the vital need for comprehensive research to discover the real effect of EPO on depression and mood disorders in women with PCOS (40).

The present study indicated no difference between the evening primrose and placebo

groups regarding the hirsutism score after the intervention. Controversial results indicate the beneficial effects of phytoestrogens and anti-androgenic compounds in treating hirsutism (41). While no significant change in hirsutism was observed in the EPO group, other factors may still play a role, including the duration of the intervention, the dosage, or the unique characteristics of the study group. Further research is needed into the pharmacodynamics of EPO and its effects on androgen levels.

Quantifying anthropometric features like waist, and hip dimensions, and weight is very important for diagnosing metabolic factors in PCOS. Our results did not show a significant difference between the evening primrose and placebo groups for these indices. Our findings contradict studies suggesting dietary supplements can affect weight and BMI in PCOS. However, Kaźmierska et al. (2022) assessed the effect of EPO supplementation on various parameters of skin status in patients undergoing isotretinoin therapy. They reported no difference between the groups in weight loss or BMI (42). This discrepancy may be due to EPO's neutral metabolic characteristics or the study's relatively short duration. Long-term studies with larger sample sizes are essential to determining the potential impact of EPO on anthropometric indices in PCOS.

Most PCOS patients have irregular menstrual cycles. Our results showed no significant difference in menstrual cycle characteristics between the evening primrose and placebo groups. EPO has been widely studied in women's health, especially in conditions like PCOS and PMS. A number of research efforts have looked into the effects of EPO supplementation on menstrual cycles in women with PCOS. While Khoo et al. (1990) found that EPO has no significant impact on menstrual cycles (43), Rezaei et al. (2021) reported that EPO can improve follicular maturation and potentially benefit women with PCOS (44). These conflicting findings highlight the need for further research to determine the effectiveness of EPO on menstrual regularity in women with PCOS.

Although EPO does not appear to have a substantial effect on the clinical symptoms of PCOS when compared to a placebo, due to the intricate nature of PCOS and the potential of phytoestrogens, additional studies are necessary. These studies should investigate different doses, longer medication durations, and larger, more homogeneous populations. Future research should also explore the mechanisms through which EPO may affect PCOS symptoms to better understand its potential therapeutic role.

The rigorous randomized controlled framework of this investigation contributed to the credibility of its conclusions. Furthermore, the adoption of validated instruments—including the Beck Depression Inventory and standardized anthropometric procedures—reinforced the overall strength and reliability of the data. Random allocation of participants to intervention and control groups helped to reduce selection bias.

This study had some limitations. The sample was small, and the follow-up period was short. . Also, this study did not consider certain lifestyle factors, such as dietary habits and exercise routines, which may influence the course of the disease. Moving forward, researchers should address these gaps by expanding sample sizes, extending follow-up intervals, and adopting more rigorous approaches to confounding variable assessment. Further, large-scale studies are recommended to investigate the effect of EPO on clinical symptoms and laboratory parameters in patients with PCOS.

Conclusion

The findings of this randomized, triple-blind clinical trial do not show a significant effect of EPO on clinical symptoms in patients with PCOS versus placebo group. In clinical practice, these results indicate that short-term, 1000 mg/day EPO supplementation should not be recommended as a standalone therapy for improving depression, hirsutism, menstrual irregularities, or anthropometric indices in women with PCOS; instead, healthcare providers should prioritize established evidence-based treatments and lifestyle modifications to avoid unnecessary costs and delays in effective care. Further large-scale studies with varying dosages, longer durations, and assessment of hormonal and metabolic laboratory parameters are warranted to clarify any potential therapeutic role of EPO in PCOS.

Declarations

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Conflicts of interest

The authors declared no conflicts of interest.

Ethical approval

Prior to enrollment, every participant provided written informed consent, and all procedures adhered to the principles set forth in the Declaration of Helsinki. The investigation was conducted in full compliance with applicable guidelines and regulatory standards.

Code of Ethics

The research protocol received formal approval from the institutional review board at Tabriz University of Medical Sciences (approval number: IR.TBZMED.REC.1401.599).

Use of Artificial Intelligence

The authors declare that no artificial intelligence (AI) tools were used in any stage of the study or manuscript preparation.

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Authors' contributions

FN, SMAG, SGH, ES, and MM contributed to the study's conception and design. FN was responsible for gathering the study data and preparing the first version of the paper, with MM providing direct oversight throughout the process. MM conducted the statistical analysis. SMAG, SGH, ES, and MM revised the manuscript. The final version of the manuscript was reviewed and endorsed by all contributing authors.

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