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CLINICAL ARTICLE

Clinical and metabolic effects of medroxyprogesterone acetate and ethinyl estradiol plus drospirenone in women with polycystic ovary syndrome

Suna Özdemir [a,*], Hüseyin Görkemli [a], Kazim Gezginç [a], Mustafa Özdemir [b], Aysel Kiyici [c]

[a] *Department of Gynecology and Obstetrics, Meram Medical Faculty, Selçuk University, Konya, Turkey*
[b] *Department of Dermatology, Meram Medical Faculty, Selçuk University, Konya, Turkey*
[c] *Department of Biochemistry, Meram Medical Faculty, Selçuk University, Konya, Turkey*

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Abstract

Objectives: To investigate the effects of treatment with medroxyprogesterone acetate (MPA), 10 days per month for 6 months, on lipid and carbohydrate metabolism in women with polycystic ovary syndrome (PCOS). *Methods:* Sixty-three women with PCOS were randomized to receive MPA or ethinyl estradiol plus drospirenone. *Results:* There were no changes in lipid or carbohydrate metabolism in the MPA group, but serum levels of luteinizing hormone ($P<0.001$) and total testosterone ($P<0.003$) significantly decreased, as did the free androgen index ($P<0.02$) and acne ($P<0.03$) and seborrhea ($P<0.04$) scores. In the ethinyl estradiol plus drospirenone group lipid and hormone values significantly increased whereas acne, seborrhea, hair loss, and Ferriman-Gallwey scores decreased. There was no statistically significant change in the total cholesterol to high-density cholesterol ratio in either group. *Conclusion:* Treatment of PCOS patients with MPA provided good menstrual cycle control, beneficial changes in hormonal values associated with hyperandrogenism, and no significant changes in lipid or carbohydrate metabolism.

1. Introduction

Polycystic ovary syndrome (PCOS) affects between 5% and 10% of women of reproductive age [1]. The exact etiology of PCOS being unknown, the preferential therapeutic strategy is controversial [2,3] and the treatment of choice may simply

* Corresponding author. S.Ü. Meram Tip Fak, Kadin Hastaliklari ve Duğum AD, 42080 Meram, Konya, Turkey. Tel.: +90 3322236234; fax: +90 3322236181.
E-mail address: snmstf@yahoo.com (S. Özdemir).

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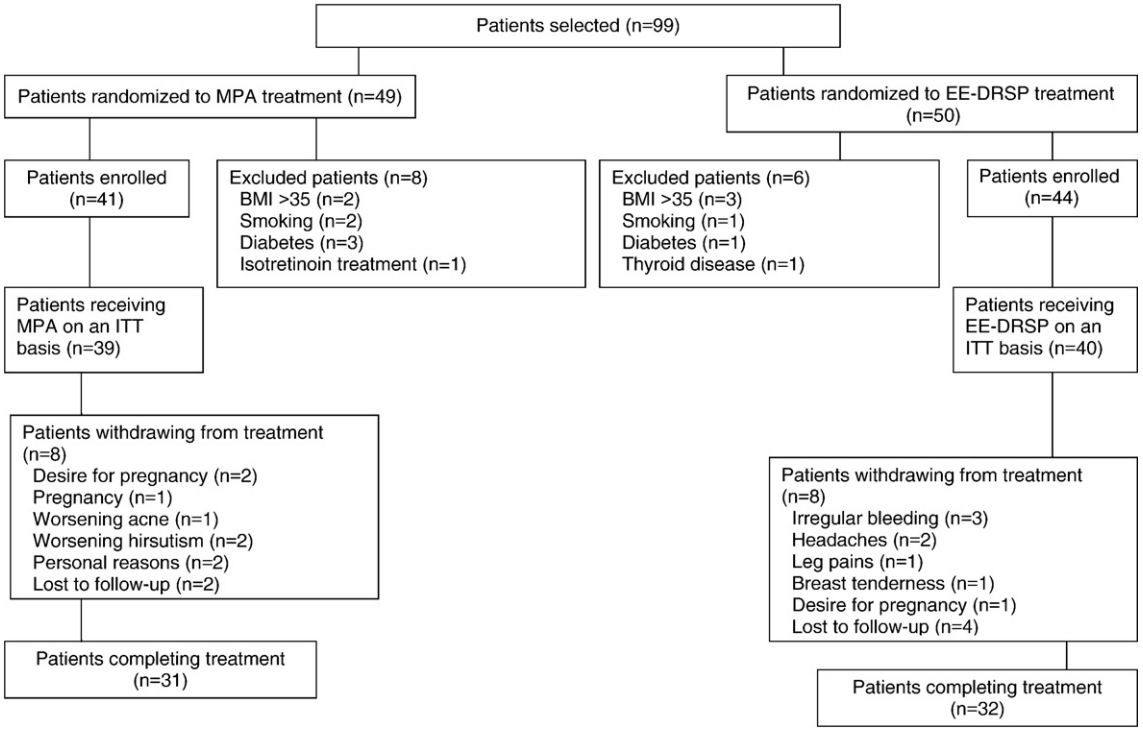

Figure 1 Flow chart of the study. EE-DRSP indicates ethinyl estradiol plus drospirenone; ITT, intention to treat; MPA, medroxyprogesterone acetate.

target the patient's main complaints [4,5]. Oral contraceptives improve menstrual regularity and some effects of hyperandrogenemia, but they affect insulin sensitivity and lipid metabolism and therefore are of special concern for women with PCOS [6–8]. Intermittent progesterone therapy can provide menstrual regulation and endometrial protection in women for whom oral contraceptives are contraindicated; but whereas the effects of medroxyprogesterone acetate (MPA) on lipid and carbohydrate metabolism are known in healthy postmenopausal women, there are limited data on the metabolic or androgenic effects of MPA in women with PCOS [9,10].

We investigated the effects of a long-term (6-month) cyclic MPA treatment in women with PCOS by comparing the metabolic, hormonal, and clinical effects of this treatment with those of a recently developed oral contraceptive consisting of ethinyl estradiol (EE) plus drospirenone. The analysis was intention to treat (ITT).

2. Materials and methods

This prospective study was conducted from November 2005 through July 2007 at the outpatient Clinic of Obstetrics and Gynecology of the Meram Medical Faculty, Meram, Konya, Turkey. Of the 99 consecutive patients with PCOS aged between 18 and 30 years who were included in the study, 63 completed the 6-month study (Fig. 1). Randomization to treatment was performed using a computer-based program. Group allocation was not concealed and the study was not blind. The diagnosis of PCOS was made according to the consensus criteria adopted in May 2003 in Rotterdam [11]. The diagnosis of PCOS was made in the presence of 2 of the 3 following criteria: 10 or more follicles measuring 2 to 8 mm in diameter in each ovary and/or an echodense stroma defined polycystic ovaries on ultrasound [12], and/or oligomenorrhea (defined as fewer than 6 menstrual periods per year or a cycle duration of at least 45 days).

Levels of prolactin, thyroid stimulating hormone, and 17-α-hydroxyprogesterone (17-α-OHP) were measured in all patients to rule out other causes of chronic anovulation. We excluded from the study patients with 17-α-OHP levels greater than 2 ng/mL; those who took hormonal medications or drugs such as atorvastatin calcium, simvastatin calcium, metformine hydrochloride, or glipizide, which are known to affect lipid metabolism, during the 2 months preceding the study; those with a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) greater than 35 or diabetes mellitus; those with contraindications to oral contraceptive use according to World Health Organization guidelines [13], as well as smokers, alcohol users, and others. The study was approved by the ethics committee of Meram Medical Faculty. Each patient gave written informed consent to participate.

The patients were randomly assigned to 2 groups. One consisted of 41 women treated with 10 mg of MPA (Farlutal; Deva, Istanbul, Turkey) for 10 days every month for 6 months, and the other consisted of 44 women treated with 30 μg of EE and 3 mg of drospirenone (Yasmin; Schering, Berlin, Germany) for 21 days, followed by an interval of 7 days, for 6 months. The study duration was based on reports that a treatment of at least 6 months was needed for optimal results [14].

Waist-to-hip ratios and BMIs were calculated, and blood samples were obtained on the second day of spontaneous menstruation for assessment of baseline levels of the following: follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2), total testosterone (TT), free testosterone, dehydroepiandrosterone sulfate (DHEAS), prolactin, and sex hormone–binding globulin (SHGB); total cholesterol (TC), high-

density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglycerides; fasting plasma glucose and insulin (I); and hemoglobin A_{1c} (HbA_{1c}). The free androgen index was calculated as TT level (in nmol/L) divided by SHBG level (in nmol/L) and multiplied by 100; insulin sensitivity was calculated as the glucose/insulin (G/I) index; and the homeostasis model assessment (HOMA) value was calculated as fasting glucose level (in mmol/L) multiplied by fasting insulin level (in μU/mL) and divided by 22.5. To unify the measurement units, the values for testosterone were converted from ng/dL to nmol/L (1 ng/dL=0.0347 nmol/L) and those for fasting glucose were converted from mg/dL to mmol/L (1 mg/dL=0.0555 mmol/L). The patients were instructed to maintain their usual eating and exercise habits and clinical, hormonal, and metabolic values were assessed at baseline and after 6 months.

The patients were requested not to depilate for at least 1 month before evaluation and the same dermatologist (M.Ö.) assessed the skin for signs of seborrhea, acne, and hair loss due to androgenetic alopecia, and determined the degree of hirsutism according to the Ferriman-Gallwey scoring system. This system distinguishes between 4 grades of hirsutism according to score: <8, no hirsutism; 8–16, mild hirsutism; 17–24, moderate hirsutism; and >25, severe hirsutism) [15]. Seborrhea, acne, and hair loss were scored on a scale of 0 to 3 (0, no symptoms; 1, mild; 2, moderate; and 3, severe) [8] by the same physician throughout the study to avoid interobserver errors.

At 9:00 AM, after overnight fasting, venous blood samples were drawn into K3 EDTA–treated tubes (Vacuette line, Greiner Bio-One, Kremsmünster, Austria) for HbA_{1c} analysis or into serum separator, clot activator tubes (Vacuette line, Greiner Bio-One) for all other assessments. The latter samples were allowed to stand 15 minutes at room temperature for clot formation and sera were then separated by centrifugation.

Glucose and lipid concentrations were determined using Synchron LX20 analyzers (Beckman Coulter, Fullerton, California, USA) with original Beckman reagents by means of the following methods: the glucose oxidase and oxygen electrode method for glucose; the timed-endpoint method for triglycerides and TC, with 3 coupled enzymatic steps using glycerol kinase, glycerophosphate oxidase, and horse radish peroxidase for triglycerides and 2 coupled enzymatic steps using cholesterol esterase and cholesterol oxidase for TC; and the direct enzymatic method without precipitation (using kits from Randox Laboratories, Crumlin, UK) for HDL cholesterol, with LDL and VLDL cholesterol concentrations calculated by the Friedewald formula. High-pressure liquid chromatography analysis for HbA_{1c} was performed using the BioRad Hemoglobin Analysing System (BioRad Laboratories, Munich, Germany); FSH, LH, E2, prolactin, DHEAS, TT, and SHBG concentrations were determined by chemiluminescent immunoassay using an Immulite 2000 immunoanalyzer (DPC–Siemens Healthcare Diagnostics, Deerfield, IL, USA) with original DPC reagents; and analysis for free testosterone was performed using a radioimmunoassay kit (BioSource Laboratories, Nivelles, Belgium).

The main outcome measure was the change in the TC/HDL ratio in patients treated with MPA. Possible changes from baseline were investigated in lipid and carbohydrate metabolism as well as in other clinical and hormonal characteristics.

The sample size was estimated on the basis of the expected TC/HDL ratio. The reported mean TC/HDL ratios are 3.9±1.1 for women with PCOS treated with EE plus drospirenone and 5.0±1.6 for those treated with MPA [16]. We estimated that a sample size of 41 patients per group would have 80% power at the 5% level to detect a difference of 1 in the mean TC/HDL ratio. Assuming a prescreening dropout of 15%, a total sample size of 99 patients was the target enrollment. The primary outcome was analyzed on an ITT basis. If a patient withdrew before the final serum evaluations, she was classified as having no change from baseline values. Of the 41 patients in the MPA group and 44 in the EE plus drospirenone

Table 1 Basal clinical, hormonal, and metabolic characteristics of the study patients [a]

Characteristic	MPA group (n=39)	EE plus drospirenone group(n=40)	*P* value
Age, y	23.4±3.9	22.7±3.8	0.62
BMI	23.6±4.4	24.3±4.8	0.56
Waist-to-hip ratio	0.7±0.5	0.8±0.5	0.06
Score			
Ferriman-Gallwey	9.6±2.9	10.4±3.6	0.37
Acne	1.0±0.8	1.1±0.8	0.72
Seborrhea	0.6±0.7	0.6±0.6	0.70
Hair loss	0.5±0.8	0.7±0.9	0.51
FSH, IU/mL	5.3±1.2	5.0±1.2	0.40
LH, IU/mL	10.3±3.4	11.0±3.1	0.26
Estradiol, pg/mL	59.2±38.4	44.9±25.1	0.11
TT, ng/dL	72.5±16.5	68.4±17.6	0.35
Free testosterone, pg/mL	3.2±0.6	3.0±0.5	0.41
SHBG, nmol/L	52.4±24.4	49.3±27.1	0.42
Free androgen index	5.7±2.7	6.0±3.2	0.95
Total cholesterol, mg/dl	171.0±25.9	163.1±32.8	0.29
HDL, mg/dL	50.6±7.9	50.0±10.6	0.80
TC/HDL ratio	3.35±0.75	3.46±0.85	0.82
LDL, mg/dL	96.5±18.5	93.8±24.3	0.62
VLDL, mg/dL	15.5±10.9	17.3±7.0	0.08
Triglycerides, mg/dL	74.6±57.4	83.4±37.7	0.06
Fasting glucose, mg/dL	88.4±5.5	91.6±7.9	0.17
Fasting insulin, μUI/mL	12.4±18.1	10.4±13.5	0.83
HbA1c, % of total Hb	5.4±0.2	5.5±0.3	0.20
Glucose/insulin ratio	12.9±7.2	17.4±16.2	0.36
HOMA value	2.7±4.0	2.3±3.1	0.90

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the height in meters squared); EE, ethinyl estradiol; FSH, follicle stimulating hormone; Hb, hemoglobin; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; TC, total cholesterol; LDL, low-density lipoprotein; LH, luteinizing hormone; MPA, medroxyprogesterone acetate; SHBG, sex hormone–binding globulin; TT, total testosterone; VLDL, very low density lipoprotein.

[a] Values are given as mean±SD.

Table 2 Changes in serum hormone values in the 2 study groups following a 6th-month treatment [a]

Variable	Baseline	6 months	*P* value
Medroxyprogesterone acetate group (n=39)			
Total testosterone, ng/dL	72.5±16.5	59.1±19.4	0.003 [b]
SHBG, μmol/L	52.4±24.4	51.8±24.4	0.76
FAI>4.5	5.7±2.7	4.7±2.5	0.02 [b]
FSH, mIU/mL	5.3±1.2	6.1±1.2	0.07
LH, mIU/mL	10.3±3.4	6.7±2.1	0.001 [b]
Estradiol, pg/mL	59.2±38.4	58.4±18.4	0.75
DHEAS, μg/dL	185.6±87.2	175.4±94.2	0.29
Ethinyl estradiol plus drospirenone group (n=40)			
Total testosterone, ng/dL	68.4±17.6	59.1±19.4	0.001 [b]
SHBG, μmol/L	49.3±27.1	116.5±54.6	0.001 [b]
FAI>4.5	6.0±3.2	2.3±2.8	0.001 [b]
FSH, mIU/mL	5.0±1.2	5.5±3.1	0.84
LH, mIU/mL	11.0±3.1	4.1±1.9	0.001 [b]
Estradiol, pg/mL	44.9±25.1	50.3±27.3	0.66
DHEAS, μg/dL	194.4±102.7	175.4±90.6	0.53

Abbreviations: DHEA, dehydroepiandrosterone sulfate; FAI, free androgen index; FSH, follicle stimulating hormone; LH, luteinizing hormone; SHBG, sex hormone binding globulin.
[a] Values are given as mean±SD.
[b] Statistically significant.

group, 31 and 32, respectively, completed the study. Calculated backwards from the number of patients who completed the study, power was 69% with a level of significance of 0.05.

Data were expressed as mean±SD. The 2-tailed *t* test, Mann-Whitney *U* test, Wilcoxon signed ranks test, and paired-sample *t* test were used for statistical analysis. $P<0.05$ was considered statistically significant.

3. Results

Of the 99 patients screened, 85 were enrolled into the study; and of these, 79 received the investigational drug on day 1 and were included in the ITT analysis. Six patients eligible for the study dropped out before receiving any study drug and therefore were not included in the ITT analysis. Patient treatment and reasons for discontinuation are shown in Fig. 1. There were no statistically significant differences in baseline clinical characteristics or hormone and lipid values between the 2 groups (Table 1).

Significant changes in hormone values were detected in both groups. In the MPA group, there were changes in serum LH and TT levels ($P=0.001$ and $P=0.003$) and in free androgen index ($P=0.02$); however, serum levels of SHBG, E_2, FSH, and DHEAS remained the same during the 6-month treatment. In the EE plus drospirenone group, changes in LH, total testosterone, and SHBG levels and in free androgen index were statistically significant ($P<0.001$ for all), but DHEAS, E_2 and FSH levels did not change (Table 2).

There were no changes in lipid levels in the MPA group. In the EE plus drospirenone group, however, there was a statistically significant increase in HDL cholesterol levels ($P=0.002$) and decreases in triglycerides and VLDL levels ($P=0.001$ and $P=0.02$). Total cholesterol and LDL cholesterol levels remained unchanged in this group. In neither group were there statistically significant changes in the TC/HDL ratio (Table 3) or in fasting glucose or insulin levels, G/I ratio, or HOMA value (Table 4).

Table 3 Changes in serum lipid levels in the 2 study groups following a 6th-month treatment [a]

Variable	Baseline	6 months	*P* value
Medroxyprogesterone acetate group (n=39)			
Total cholesterol, mg/dL	171.0±25.9	175.1±27.7	0.54
HDL, mg/dL	50.6±7.9	52.6±11.4	0.17
TC/HDL ratio	3.35±0.75	3,35±1.12	0.87
LDL, mg/dL	96.5±18.5	96.0±21.1	0.71
VLDL, mg/dL	15.5±10.9	14.9±6.6	0.20
Triglycerides, mg/dL	74.6±57.4	73.4±40.1	0.29
Ethinyl estradiol plus drospirenone group (n=40)			
Total cholesterol, mg/dL	163.1±32.8	162.1±27.7	0.64
HDL, mg/dL	50.0±10.6	59.6±16.7	0.002 [b]
TC/HDL ratio	3.46±0.85	3.01±0.81	0.61
LDL, mg/dL	93.8±24.3	96.0±21.1	0.13
VLDL, mg/dL	20.7±7.3	28.0±4.0	0.02 [b]
Triglycerides, mg/dL	83.4±37.7	93.4±40.1	0.001 [b]

Abbreviations: HDL, high density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol; VLDL, very low density lipoprotein.
[a] Values are given as mean±SD.
[b] Statistically significant.

Waist-to-hip ratio, BMI, hair loss, and hirsutism scores did not change significantly in the MPA group, where there were increases in acne and seborrhea scores. There were significant decreases in hirsutism and acne scores ($P=0.001$ for both) in the EE plus drospirenone group, where decreases in seborrhea and hair loss scores also reached statistical significance (Table 5).

4. Discussion

We found that a 6-month treatment with MPA improved the androgen index as well as LH and TT levels in women with

Table 4 Changes in carbohydrate metabolism in the 2 study groups following a 6th-month treatment [a]

Variable	Baseline	6 months	*P* value
Medroxyprogesterone acetate group (n=39)			
Fasting glucose, mg/dL	88.4±5.5	87.7±4.5	0.52
Fasting insulin, μUI/mL	12.4±18.1	7.9±3.4	0.42
Glucose/insulin ratio	12.9±7.2	13.4±7.3	0.96
HOMA	2.7±4.0	1.7±0.8	0.45
Ethinyl estradiol plus drospirenone group (n=40)			
Total cholesterol, mg/dL	171.0±25.9	175.1±27.7	0.54
Fasting glucose, mg/dL	91.6±7.9	87.7±4.5	0.27
Fasting insulin, μUI/mL	10.4±13.5	12.4±5.7	0.88
Glucose/insulin ratio	17.4±16.2	13.2±7.3	0.41
HOMA	2.3±3.1	1.8±1.3	0.85

Abbreviations: HOMA, homeostasis model assessment.
[a] Values are given as mean±SD.

Table 5 Anthropometric and skin manifestation changes in the 2 study groups following a 6th-month treatment [a]

Variable	Baseline	6 months	*P* value
Medroxyprogesterone acetate group (n=39)			
BMI	23.6±4.4	23.8±4.4	0.82
Waist-to-hip ratio	0.7±0.5	0.8±0.4	0.70
Score			
Ferriman-Gallwey	9.6±2.9	9.1±2.6	0.13
Acne	1.0 (0–2)	1.0 (0–3)	0.03 [b]
Seborrhea	1.0 (0–3)	1.0 (0–3)	0.04 [b]
Hair loss	1.0 (0–3)	1.0 (0–3)	0.50
Ethinyl estradiol plus drospirenone group (n=40)			
BMI	24.3±4.8	24.1±4.6	0.30
Waist-to-hip ratio	0.8±0.5	0.8±0.4	0.50
Score			
Ferriman-Gallwey	10.4±3.6	7.5±1.9	0.001 [b]
Acne	1.0 (0–2)	0.0 (0–1)	0.001 [b]
Seborrhea	1.0 (0–3)	1.0 (0–2)	0.04 [b]
Hair loss	1.0 (0–3)	1.0 (0–3)	0.02 [b]

[a] Values are given as mean±SD or median (range).
[b] Statistically significant.

PCOS, but that this treatment had no effect on their lipid or carbohydrate metabolism. We also found that a treatment of the same duration with EE plus drospirenone improved hormone and lipid levels, accompanied with a decrease in hirsutism, acne, seborrhea, and hair loss scores. The reproductive, metabolic, and cardiovascular components of PCOS offer a broad spectrum of therapeutic options, all of which having both beneficial and negative clinical and metabolic effects. Although oral contraceptives are commonly given as first-line therapy, they may induce or exacerbate the insulin resistance often present in women with this syndrome [17,18]. These agents currently contain low levels of estrogen, their progesterone component being the main determinant of their metabolic effects [19]. The role of progesterone in the pathogenesis of PCOS is not known, but it has been suggested that progesterone deficiency might facilitate the development of hypothalamic and pituitary abnormalities observed in women with this syndrome [20]. Although progestins provide good cycle control with endometrial protection, published data about clinical and metabolic effects of these agents are few [16,21].

A second-generation progestin, MPA, is used to regulate the menstrual cycle of women with PCOS [22]. Alone or in combination with estrogen, MPA was found to decrease insulin sensitivity significantly in an animal study [19,22]; however, in a study with postmenopausal women, MPA combined with estrogen had a small effect on insulin and glucose levels [10]. In a study with a small sample size by Bagis et al. [21], short-term treatment with MPA (1 cycle) had a beneficial effect on HOMA values and improved insulin sensitivity in women with PCOS. Yet, a 6-month treatment did not modify carbohydrate metabolism in the present study, although there was a nonsignificant decrease in fasting insulin and a nonsignificant increase in the mean G/I ratio and HOMA value. Similarly, Villaseca et al. [16] recently reported that a 3-month MPA treatment had no effect on fasting glucose and insulin levels or on the G/I ratio. Mean fasting insulin levels increased in our EE plus drospirenone group, but the mean G/I ratio decreased and the change in HOMA value did not reach statistical significance.

Although treatment with MPA did not lead to statistically significant changes in lipid values, there was a nonsignificant increase in total cholesterol and HDL cholesterol levels. On the other hand, the TC/HDL ratio and triglyceride, LDL cholesterol, and VLDL cholesterol levels remained unchanged. Bagis et al. [21] found a statistically significant increase in LDL cholesterol level after 1 cycle of MPA treatment. However, treatment with MPA changed none of the lipoprotein values either in the 3-month study by Villaseca et al. [16] or in our study; and although these authors found a nonsignificant decrease in triglyceride levels, we did not detect such a decrease. The reason for this discrepancy may lie in our study's longer duration and larger sample size. In addition, our participants had a lower mean BMI. Many studies have reported that oral contraceptives containing different progestins produced similar changes in lipoproteins values such as increases in total cholesterol and HDL cholesterol levels [8,19]. Although all lipoprotein values remained within the normal range in our study, there were statistically significant increases in triglyceride as well as HDL and VLDL cholesterol levels following treatment with EE plus drospirenone.

Regarding hormone levels, a 6-month treatment with MPA led to statistically significant decreases in LH and TT levels as well as in free androgen index. Following this treatment there were no changes in SHBG, FSH, E2, or DHEAS levels. The mechanism of action of MPA is slightly different from that of oral contraceptives. It leads to significant LH suppression and a decrease in testosterone production. In addition, testosterone clearance from the circulation is increased owing to the induction of liver enzyme activity [19,23]. The hormonal changes observed in the present study following treatment with MPA are in agreement with those described in the literature. However, these changes were not observed after 3 months [16]. Consistent with the literature, a statistically significant decrease in TT and increase in SHBG levels were observed in our study following treatment with EE plus drospirenone.

Hirsutism, acne, seborrhea, and androgenetic alopecia are the skin manifestations of PCOS, and androgens play an important role in their development. Reports on the effectiveness of oral contraceptives against these manifestations are conflicting [4,24]. In this study, significant improvements in acne and seborrhea scores were observed after MPA treatment but Ferriman-Gallwey and hair loss scores did not change. Androgens prolong the anagen phase of body hair (normal range, 2–6 years) while shortening the anagen phase of scalp hair (normal range 2–6 months). For this reason, the 6th-month treatment duration with MPA may not have been sufficient to change this cascade, and a longer use of MPA may be effective in diminishing hirsutism in women with PCOS. In this study as in others [8,25], statistically significant improvement was achieved in Ferriman-Gallwey, hair loss, acne, and seborrhea scores following a 6-month treatment with EE plus drospirenone.

In conclusion, treatment with MPA provided good control of the menstrual cycle and important changes in serum levels of hormones associated with hyperandrogenism in women with PCOS, but no significant change in the metabolism of lipids and carbohydrates. Treatment with EE plus drospirenone induced significant changes in hormone and lipid values and skin

manifestations, and treatment with MPA can be considered to treat menstrual disorders in patients without dyslipidemia or hyperinsulinemia. In addition, treatment with MPA may improve the skin manifestations related to hyperandrogenism and may also be administered to patients for whom oral contraceptives are contraindicated.

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