Adding Metformin to the Oral Contraceptive Treatment for Hirsutism has No Additional Effect on Ferriman-Gallwey Scores in Hirsute Women with PCOS: A Randomized Controlled Study

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OBJECTIVE: To analyze the additional benefits of adding metformin to the oral contraceptive pill (OCP) treatment in lean women with PCOS.

STUDY DESIGN: After a baseline work-up including BMI, waist-to-hip ratio, Ferriman-Gallwey (FG) score, serum hormone, SHBG, fasting glucose and insulin levels, 28 nonobese women with PCOS were randomized either to the OCP or to the OCP-plus-metformin treatment. At the end of the 4-month follow-up period, subjects were re-evaluated.

RESULTS: The two groups were similar at baseline. The effects of the two treatments on the FG score were similar. Subjects, who received OCP-plus-metformin had significantly higher reductions in serum androstenedione than those, who received OCP alone. Fasting glucose-to-insulin ratio improved significantly in the OCP-plus-metformin group, while OCP treatment alone did not cause any significant change.

CONCLUSIONS: Adding metformin to the OCP treatment may result in additional benefits, but does not improve hirsutism over the OCP treatment alone.
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Key Words: Metformin, Hirsutism, Oral contraceptive, Polycystic ovary syndrome, Cyproterone acetate

Hirsutism, the presence of terminal (coarse) hairs in females in a male-like pattern, affects between 5% and 10% of women surveyed.[1] The presence of hirsutism is extremely distressing to patients, with a significant negative impact on their psychosocial development.[2] In the majority of patients hirsutism should be considered as a sign of other conditions [e.g., the polycystic ovary syndrome (PCOS), androgen-secreting tumors, nonclassic adrenal hyperplasia, or syndromes of severe insulin resistance], rather than an isolated disorder.[3] Approximately, 5-15% of hirsute women do not have ovulatory abnormalities and have normal levels of circulating androgens, i.e. idiopathic hirsutism.[3] Sixty-five to 85% of the rest of the hirsute women are diagnosed as having PCOS.[4] Therefore, PCOS is the most common cause of hirsutism. It is characterized by chronic anovulation and hyperandrogenism. In addition to these major features, insulin resistance and compensatory hyperinsulinemia are intrinsic features of the disorder. At least 50% to 80% of women with PCOS are obese.[5] However, several investigators have demonstrated that even lean women with PCOS exhibit a form of insulin resistance out of proportion to body mass index (BMI), underscoring the universality of insulin resistance in women with PCOS and the important role hyperinsulinemia has in the pathophysiology of this syndrome.[6]

The pathophysiology of insulin resistance in women with PCOS remains undetermined. However, hyperandrogenism does not appear to cause insulin resistance. Suppression of ovarian and/or adrenal androgenism does not diminish insulin resistance.[7] On the contrary, hyperinsulinemia does appear to cause hyperandrogenism.[8] Evidence consistently indicates that insulin, in synergy with LH, has a direct ovarian effect to modulate ovarian androgen secretion. [9]

Metformin is an oral biguanide antihyperglycemic drug used for decades for the treatment of type 2 diabetes mellitus (DM). Recent studies have indicated that this drug improves metabolic abnormalities, decreases androgen levels, and improves menstrual pattern and ovulatory function.[10] Hirsutism scores also have been reported either to improve in some studies or have no change in the others.[11-14]

There is not enough evidence to suggest the insulin-reducing medications as first-line therapy for hirsute women with PCOS. First, not all women with PCOS are insulin resistant, and it is not clear that insulin resistance is the primary defect of the heterogeneous disorder of PCOS. The most popular treatments for hirsutism due to PCOS are oral contraceptive pills (OCPs) and/or antiandrogens, such as spironolactone and flutamide. OCPs diminish ovarian androgenism. However, they do not improve insulin resistance, and further may induce impairment of glucose tolerance.[15,16] Hyperinsulinemia does appear to cause hyperandrogenism. Therefore, we hypothesized that comparing with the OCP treatment alone, treatment of insulin resistance by an insulin-lowering drug combined with the OCP treatment may further diminish hy-

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perandrogenism, and may have additional benefits in the treatment of hirsutism due to PCOS.

To test this hypothesis, we designed this study to compare the clinical and biochemical effects of the two treatment modalities; [1] the commonly used ethinyl estradiol (EE) - cyproterone acetate (CA) OCP and [2] metformin added to this OCP, in lean women with hirsutism due to PCOS.

Materials and Methods

Women presenting to the Hirsutism Outpatient Clinic were evaluated for the etiology of hirsutism, and those, who were lean and had hirsutism due to PCOS, were included into the study. Polycystic ovary syndrome was defined as the presence of [1] bilateral polycystic ovaries on ultrasound examination, [2] chronic oligomenorrhea (<6 menstrual periods in the previous year) or amenorrhea, and [3] manifestations of hyperandrogenism and/or hyperandrogenemia, such as hirsutism; acne; elevated serum testosterone and/or androstenedione and/or free testosterone levels. All the women were either normal weight or thin (BMI, 20.8-25.9 kg/m^2) and hirsute (a hirsutism score of more than 8, according to Ferriman and Gallwey[1]).

All the women were euthyroid (serum TSH level, 0.35-5.5 mU/l) and had normal prolactin levels (serum prolactin level, 3.4-24 mg/l). Their serum testosterone levels were <7 nmol/l, and DHEAS levels were <19 mmol/l. If the basal serum 17OH-progesterone (17OH-P) level was >6 nmol/l, an ACTH stimulation test was done to exclude patients with late-onset congenital adrenal hyperplasia. A serum cortisol level of >140 nmol/l after an overnight dexamethasone suppression test also was an exclusion criterion. Women were excluded from the study if an adnexal mass was noted on pelvic sonography.

After 3 days on a high carbohydrate diet (300 g/day) and an overnight fast of 10-12 h, all subjects underwent an oral glucose tolerance test (OGTT; a load of 75 g glucose in 300 mL water). Venous blood samples were drawn at 0, 30, 60, and 120 min for plasma glucose determination. Women, who were found to have diabetes according to the new American Diabetes Association criteria in 1997, were excluded from the study.[17] Women, who had any other known endocrinologic disease and those taking drugs known to affect carbohydrate metabolism and OGTT results during the 6 months preceding the study, were also excluded.

Medical histories were taken, and all subjects underwent gynecologic examination and pelvic ultrasonography. Weight and height were obtained and BMI (weight [kg]/ height $[m]^2$) was calculated. Waist and hip circumferences were measured to the nearest centimeter with a soft tape at the narrowest part of the torso and at the widest part of the gluteal region, and waist-to-hip ratio (WHR) was calculated.

All laboratory investigations and ultrasound examinations were performed in the early follicular phase (days 3-5) of spontaneous bleeding or withdrawal bleeding induced with medroxyprogesterone acetate at baseline or with the OCP after the follow-up period. All ultrasound examinations were performed either transabdominally or transvaginally (3.5-MHz and 5-MHz sector probes, respectively; GE Logiq 200 Pro, GE Medical Systems, Milwaukee, WI). Polycystic-appearing ovaries were defined sonographically as the presence of multiple (>10), small (2 - 8 mm in diameter) follicles in the periphery (in one plane) and increased stromal echogenicity as described by Adams et al.[18] The study was approved by the Institutional Review Board at Marmara University, and written informed consent was obtained from each subject.

After baseline clinical (BMI, WHR and Ferriman-Gallwey [FG] score), endocrinologic (FSH, LH, testosterone, free testosterone, androstenedione, 17OH-P, DHEAS and SHBG) and metabolic (fasting glucose and insulin) workups, the subjects were randomized to either the OCP group or to the OCP-plus-metformin group. Women in the OCP group were prescribed EE, 35 mg, and CA, 2 mg, (Diane 35, Schering AG, Berlin, Germany) for 21 days per each month followed by a 7-day pill-free period. Women in the OCP-plus-metformin group were prescribed metformin 500 mg tid orally (for the first 15 days, 500 mg bid for adequate compliance; Glucophage, Ilsan and Iltas Pharmaceuticals, Istanbul, Turkey) in addition to the above-mentioned pill. The women were prospectively followed for 4 months, and at the end of this follow-up period, the baseline evaluation was repeated.

Randomization was produced from a computer generated random list, where pair and odd numbers allocated OCP and OCP-plus-metformin treatments, respectively.

Blood samples were obtained through venipuncture, and centrifuged within 2 hours after withdrawal. Serum was stored at -20°C; it was assayed for FSH, LH, testosterone, SHBG and DHEAS with chemiluminescent immunoassay kits (FSH, LH and testosterone kits were provided by Roche Diagnostics Corporation [Indianapolis, IN]; SHBG and DHEAS kits were provided by Diagnostic Products Corporation [Los Angeles, CA]), and for free testosterone, androstenedione and 17OH-P with commercially available RIA kits (17-OHP kit was provided by Diagnostic Systems Laboratories, Inc. [Webster, TX]; Free testosterone and androstenedione kits were provided by Diagnostic Products Corporation [Los Angeles, CA]).

The average intra-assay coefficients of variation (CVs) were 1.5% for FSH, 0.7% for LH, 1.4% for testosterone, 9% for free testosterone, 6.1% for SHBG, 9.5% for DHEAS, 6.5% for androstenedione, and 4.1% for 17-OHP. The average total CVs were 3.8% for FSH, 1.6% for LH. The average inter-assay CVs were 2.2% for testosterone, 8.5% for free testosterone, 8% for SHBG, 13% for DHEAS, 10% for androstenedione, and 6.8% for 17OH-P.

Table 1. Clinical and biochemical characteristics of women in both groups.

	OCP group (n = 14)			OCP + metformin group (n = 14)			Effect of treatment
	Baseline	After	*P* within group	Baseline	After	*P* within group	*P* between groups
Age (years)	22.54±5.88 (18.98-26.09)			23.50±6.59 (18.79-28.21)			
BMI (kg/m^2)	21.81±1.58 (20.75-22.87)	21.76±2.20 (20.19-23.34)	0.89	23.54±2.47 (21.78-25.30)	23.24±2.86 (20.84-25.63)	0.06	0.13
Waist / hip ratio	0.81±0.04 (0.79-0.84)	0.80±0.04 (0.77-0.82)	0.14	0.84±0.07 (0.78-0.89)	0.82±0.07 (0.76-0.87)	0.18	0.31
FG score	13.92±3.84 (11.60-16.24)	12.15±3.46 (10.06-14.24)	<0.001[a]	12.00±2.60 (10.00-14.00)	10.33±2.12 (8.70-11.96)	<0.001[a]	0.19
LH (IU/l) / FSH (IU/l) ratio	1.91±0.60 (1.55-2.27)	1.27±0.54 (0.93-2.27)	0.003[a]	1.64±0.39 (1.36-1.92)	1.11±0.51 (0.68-1.54)	0.26	0.57
T (nmol/l)	2.62±1.61 (1.64-3.59)	1.44±1.49 (0.44-2.44)	0.04[a]	2.71±1.67 (1.43-3.99)	1.44±1.40 (0.15-2.73)	0.04[a]	0.68
Free T (pg/mL)	11.56±5.09 (7.92-15.20)	7.78±4.46 (4.59-10.97)	0.01[a]	13.19±3.27 (10.68-15.71)	8.02±3.11 (5.42-10.62)	0.04[a]	0.64
A (nmol/l)	11.95±1.74 (10.61-13.29)	5.82±3.35 (3.24-8.40)	0.003[a]	10.72±3.63 (80121-13.32)	3.46±1.32 (2.36-4.56)	0.002[a]	0.04[a]
17OH-P (nmol/l)	3.40±1.66 (2.21-4.59)	2.31±1.01 (1.54-3.08)	0.04[a]	2.48±1.03 (1.74-3.22)	3.32±3.04 (1.14-5.50)	0.47	0.87
DHEAS (µmol/l)	8.70±2.45 (6.95-10.45)	8.25±2.76 (6.39-10.11)	0.49	7.56±2.11 (5.80-9.32)	9.97±2.82 (7.36-12.58)	0.05	0.91
SHBG (nmol/l)	44.86±10.50 (36.79-52.93)	86.90±25.96 (68.33-105.47)	0.02[a]	51.11±21.04 (33.52-68.70)	102.75±37.15 (71.69-133.81)	0.04[a]	0.20
Glucose (mmol/l) / insulin (pmol/l) ratio	0.047±0.043 (0.020-0.074)	0.050±0.034 (0.027-0.072)	0.91	0.044±0.031 (0.021-0.068)	0.050±0.023 (0.032-0.067)	0.009[a]	0.66

[a] P < 0.05

Results are expressed as mean ± SD with the 95% confidence intervals in parentheses.

BMI = body mass index; FG = Ferriman-Gallwey; T = testosterone; A = androstenedione; 17OH-P= 17-hydroxyprogesterone; SHBG = sex hormone binding globulin.

Plasma glucose concentrations were measured with the glucose oxidase technique using an auto-analyzer (BM/Hitachi 917, Boehringer Mannheim GmbH, Mannheim, Germany). Serum insulin concentrations were measured by chemiluminescent enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA). Intra-assay and total CVs for different values of insulin were between 3.8 and 4.8%, and 4.2 and 7.6%, respectively.

Differences in baseline characteristics between the two groups were analyzed by Student's t test. Clinical, endocrine and metabolic features were analyzed by repeated measures analysis of variance. In this repeated measures model, simple contrasts were used to test differences between baseline and after-treatment values. SPSS, Inc. Release 10.0 (SPSS, Inc., Chicago, IL) was used for these analyses. Values are expressed as 'mean±SD', and P <0.05 was considered statistically significant.

Results

Twenty-eight women, 14 in each group and aged 16-35 yr, were eligible for the study. All of them accepted to participate in the trial, and were randomized. Table 1 shows the clinical and biochemical characteristics of women in both groups, at baseline and after treatment. At baseline, all the clinical and biochemical parameters were similar between the two groups (P>0.05).

Two patients in OCP-plus-metformin group reported mild nausea and gastrointestinal problems that did not necessitate discontinuation of the treatment. After treatment, FG score, serum testosterone, free testosterone and androstenedione levels decreased, and SHBG levels increased significantly in both groups (Table 1; Figures I and II). These changes were comparable between groups, except the androstenedione levels. Subjects, who received OCP-plus-metformin, had significantly higher reductions in serum androstenedione than those, who received OCP alone (P=0.04 between groups for androstenedione; Table 1; Figure II).

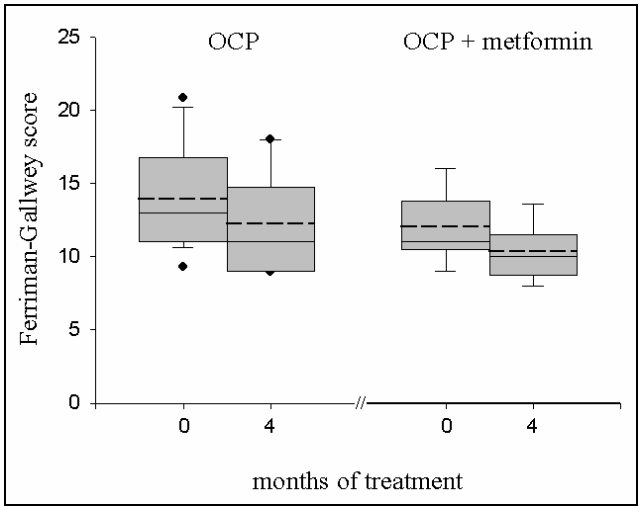

Figure I. Baseline and after-treatment Ferriman-Gallwey scores in the two groups. Data are presented as box-plots. The solid and dashed lines within the box represent the median and mean, respectively. The lower and upper boundaries of the box indicate the 25th and 75th percentiles, respectively. The 10th and 90th percentiles are indicated by error bars. OCP=oral contraceptive pill.

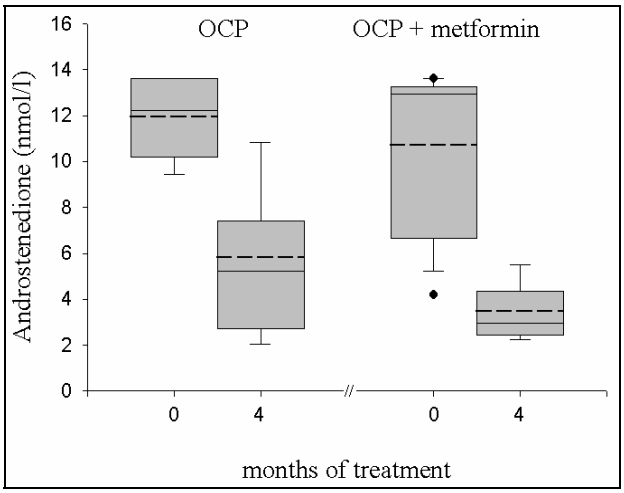

Figure II. Baseline and after-treatment serum androstenedione levels in the two groups. Data are presented as box-plots. The solid and dashed lines within the box represent the median and mean, respectively. The lower and upper boundaries of the box indicate the 25th and 75th percentiles, respectively. The 10th and 90th percentiles are indicated by error bars. OCP=oral contraceptive pill.

After treatment, fasting glucose-to-insulin ratio improved significantly in the OCP-plus-metformin group (P=0.009), while OCP treatment alone did not cause any significant change in the other group (Table 1; Figure III). However, this difference between groups did not reach significance (Table 1).

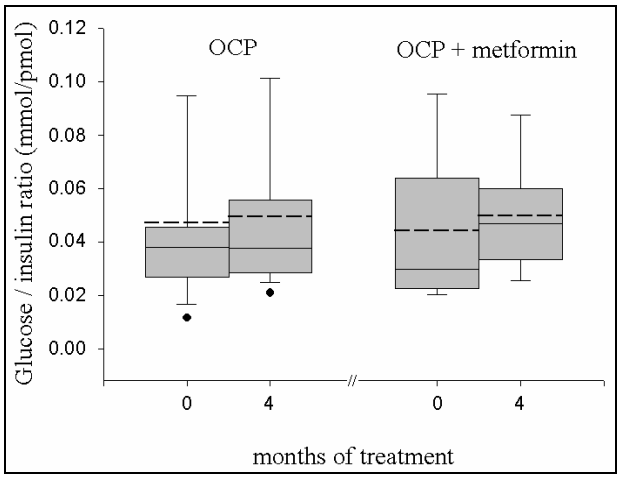

Figure III. Baseline and after-treatment fasting glucose-to-insulin ratios in the two groups. Data are presented as box-plots. The solid and dashed lines within the box represent the median and mean, respectively. The lower and upper boundaries of the box indicate the 25th and 75th percentiles, respectively. The 10th and 90th percentiles are indicated by error bars. OCP=oral contraceptive pill.

Discussion

To our knowledge, this is the first study on the effect of adding metformin to the OCP treatment on hirsutism in lean and hirsute women with PCOS. Our data showed that adding metformin may have additional benefits in the treatment of hyperandrogenemia in these women. However, our results suggest that these benefits are not sufficient to improve hirsutism better than the OCP treatment alone during the 4-month follow-up period. Benefits from adding metformin were a higher decrease in serum androstenedione levels and a higher increase in the fasting glucose-to-insulin ratio, although the latter did not reach significance.

Morin-Papunen et al. have administered metformin to 20 women with PCOS for 4-6 months.[13] They reported no significant change in the hirsutism scores during treatment (Baseline and after-treatment hirsutism scores have not been mentioned in the study). In their following study, 18 obese women with PCOS were randomized either to metformin or to EE-CA OCP treatments, and followed for 6 months.[14] The FG score did not change in the metformin group (Baseline [mean±SE]:10.3±1.9; after treatment [mean±SE]: 10.0±1.9), while decreased significantly in the OCP group (Baseline [mean±SD]: 9.0±2.1; after treatment [mean±SD]: 7.4±1.7, P<0.01).[14] However, the authors have recruited all obese subjects with PCOS, including those, who did not have hirsutism, in both of their studies,[13,14] and have not analyzed the effect of treatment on hirsute subjects, separately.

Pasquali et al. also followed 20 obese women with PCOS, after the subjects were randomized either to metformin or to placebo for 6 months.[12] They have reported that the FG score decreased significantly in those treated with metformin (Baseline [mean±SD]: 14.8±7.5; after treatment [mean±SD]: 12.9±7.6, P<0.05), but not in those taking placebo.[12] Nine of the 12 subjects in the metformin group were hirsute in their study.[12] Regarding the effect of metformin on hirsutism in women with PCOS, the difference between the above two studies[13,14] and the latter study 12 may be due to the difference in the study populations. The subjects in the latter study 12 had higher baseline FG scores (means: 14.8 versus 9.0).

Kolodziejczyk et al. have administered metformin to 35 women with PCOS and hyperinsulinemia for 3 months, and reported a significant decrease in hirsutism score at the end of treatment (Baseline [mean±SE]: 8.11±0.73; after treatment [mean±SE]: 7.86±0.7, P<0.05).[11]

These studies suggest that metformin may be helpful in treating hirsutism in selected women with PCOS, e.g. hirsute and/or hyperinsulinemic women with PCOS. However, there is still not enough evidence to suggest metformin alone as the first line treatment. We analyzed the effects of adding metformin to the OCP treatment, which is a common medical treatment for hirsutism, in lean and hirsute women with PCOS. We observed that adding metformin caused a higher decrease in androstenedione levels. Similar changes in serum androstenedione levels have been reported previously with metformin treatment in women with PCOS.[19,20] However, we observed that this effect of adding metformin on androgens is not enough to improve hirsutism over the OCP treatment alone.

In our study, fasting glucose-to-insulin ratio, which is a reliable indicator of insulin sensitivity in women with PCOS, did not change significantly in the OCP group. However, it increased significantly in the OCP-plus-metformin group.

This improvement may be a good reason to combine metformin and OCP treatments, at least in selected patients, since evaluation of the effect of OCPs on insulin sensitivity, using the euglycemic hyperinsulinemic clamp technique, has shown a significant decrease in insulin sensitivity during 3-6 months of treatment.[21,22] One study,[23] using the euglycemic clamp in PCOS women treated with EE-CA OCP, showed a significant decrease in insulin sensitivity; but in other studies, either no effects on circulating insulin concentrations and insulin resistance, or impairment of carbohydrate metabolism, have been observed.[24,25] Therefore, EE-CA OCP treatment may adversely affect insulin sensitivity in women with PCOS, and should be used with caution in women with PCOS, especially in those subjects with a familial disposition to type 2 DM.

In conclusion, adding metformin to the OCP treatment may have no beneficial effect on FG scores. However, this treatment modality may prevent any potential risk of insulin resistance associated with the OCP treatment, and/or treat an existing insulin resistance.

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