Comparison of effects of 3 mg drospirenone plus 20 μg ethinyl estradiol alone or combined with metformin or cyproterone acetate on classic metabolic cardiovascular risk factors in nonobese women with polycystic ovary syndrome

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Objective: To evaluate the effects of a pill with drospirenone (3 mg) plus ethinyl E_2 (20 μg) (DRP/20EE) alone or associated with metformin or cyproterone acetate (CPA) on some metabolic cardiovascular risk factors in women with polycystic ovary syndrome (PCOS).
Design: Randomized, open-label clinical trial.
Setting: Academic medical clinic.
Patient(s): Forty-eight hirsute women with PCOS.
Intervention(s): Patients were randomized to treatment with DRP/20EE or with DRP/20EE plus metformin (1,500 mg/d) or with DRP/20EE plus CPA (12.5 mg/d, 10 days per cycle) for 6 months.
Main Outcome Measure(s): Blood pressure, lipid profile, and indexes of glucose tolerance and insulin sensitivity were assessed before and after 6 months of treatment.
Result(s): Body mass index and blood pressure were not modified by any treatment. Treatment with DRP/EE20 did not change the lipid profile; DRP/EE20 plus metformin significantly increased high-density lipoprotein cholesterol concentrations; DRP/EE20 plus CPA significantly increased triglycerides and total cholesterol. The area under the curve for insulin was significantly decreased by DRP/EE20 and DRP/EE20 plus metformin, but it was significantly increased by DRP/EE20 plus CPA. Treatment with DRP/EE20 plus CPA significantly increased the homeostasis model assessment of insulin resistance index and significantly reduced the glucose to insulin ratio index. Treatment with DRP/EE20 significantly increased the glucose to insulin ratio index.
Conclusion(s): Treatment with DRP/EE20 improved insulin sensitivity in hirsute women with PCOS, with no deterioration of lipid profile. This effect was not ameliorated by the addition of metformin. The positive metabolic effects of DRP are abolished by the concomitant use of CPA. (Fertil Steril® 2010;94:1793–8. ©2010 by American Society for Reproductive Medicine.)

Key Words: PCOS, drospirenone, metformin, cyproterone acetate

Women with polycystic ovary syndrome (PCOS) show an increased risk of atherosclerosis and elevated blood pressure (1, 2) as a consequence of hyperandrogenism and the insulin-resistant metabolic milieu. A prothrombotic state (3, 4) and endothelial dysfunction (5) have also frequently been observed in these subjects. At present, along with dietary-induced weight loss, the administration of insulin sensitizers represents the first line of therapeutic options for women with PCOS. In particular, metformin, the most commonly used insulin sensitizer, produced favorable outcomes on the metabolic derangements of women with PCOS, not only in obese but also in insulin-resistant, normal-weight subjects (6, 7). The metabolic effects are associated with positive outcomes on menses abnormalities, ovulation rate, and circulating androgen levels (8–10). The addition of metformin to oral contraceptives (OCs) has been proposed (11).

Oral contraceptives are also a common treatment for PCOS and have a long history of use in these patients. The goal of this approach was to obtain a regular menstrual cycle and to improve the clinical signs of hyperandrogenism (12–14). In some women with PCOS with hirsutism, OCs must be combined with high doses (12.5–100 mg/d) of cyproterone acetate (CPA) or with flutamide for better suppression of hair growth (15–18). Because OCs may activate the coagulation system and their use may be associated with a deterioration of carbohydrate metabolism and lipid profile, at present the use of OCs in women with PCOS is still under scrutiny (19). However, the metabolic effects of pills are extremely variable, depending on the dose of ethinyl E_2 (EE) and on the type of progestin associated. Drospirenone (DRP) is a progestin with antiandrogenic and antimineralcorticoid activity (20), and combined with EE it is effective in decreasing hirsutism and T levels and, more significantly, increasing sex hormone–binding globulin (SHBG) levels in women with PCOS (21, 22).

Considering that OCs may exacerbate the metabolic profile of women with PCOS, it is important to investigate whether a low-

Received August 10, 2009; revised October 6, 2009; accepted October 8, 2009; published online November 19, 2009.
F.F. has nothing to disclose. D.P. has nothing to disclose. V.L. has nothing to disclose. D.P. has nothing to disclose. M.G. has nothing to disclose. A.R.G. has nothing to disclose.
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TABLE 1

Baseline characteristics of patients randomized to receive DRP/EE20 alone or combined with metformin or CPA.

Parameter	DRP/EE20 (n = 16)	DRP/EE20 + metformin (n = 15)	DRP/EE20 + CPA (n = 16)
Age (y)	24.3 ± 2.9	23.6 ± 3.6	24.1 ± 4.8
BMI (kg/m^2)	24.7 ± 3.0	24.7 ± 3.9	23.8 ± 2.5
WHR	0.8 ± 0.2	0.8 ± 0.1	0.8 ± 0.1
Total T (ng/mL)	0.7 ± 0.3	0.7 ± 0.2	0.8 ± 0.3
SHBG (ng/mL)	29.5 ± 12.3	23.7 ± 10.9	31.0 ± 10.3
FAI	10.3 ± 8.2	11.0 ± 4.1	10.7 ± 8.0
Androstenedione (ng/mL)	3.1 ± 1.2	2.5 ± 0.9	3.5 ± 1.0
Total cholesterol (mg/dL)	149.0 ± 13.2	160.4 ± 33.7	165.4 ± 25.2
HDL cholesterol (mg/dL)	53.1 ± 6.6	51.8 ± 15.3	51.7 ± 9.3
LDL cholesterol (mg/dL)	86.6 ± 13.0	85.7 ± 27.3	91.1 ± 20.0
Triglycerides (mg/dL)	67.9 ± 15.6	90.1 ± 16.2	84.3 ± 25.3
Fasting glucose (mg/dL)	76.1 ± 7.9	78.4 ± 9.2	78.3 ± 5.3
Fasting insulin (μU/mL)	9.4 ± 3.8	9.3 ± 4.3	7.4 ± 3.4
AUC glucose (mg/dL × 120 min)	12,291 ± 2,325	13,299 ± 2,364	12,200 ± 2,443
AUC insulin (μU/mL × 120 min)	5,490 ± 3,057	5,446 ± 3,468	4,877 ± 2,277
HOMA-IR	1.9 ± 0.7	1.8 ± 1.1	1.4 ± 0.6
G/I	8.6 ± 3.5	10.2 ± 4.2	12.1 ± 3.9
Systolic blood pressure (mm Hg)	112.1 ± 8.1	116.5 ± 8.5	112.7 ± 12.3
Diastolic blood pressure (mm Hg)	71.4 ± 3.8	73.5 ± 5.3	75.9 ± 10.4

Note: Data are expressed as mean ± SD. The Kruskal-Wallis test was performed to analyze the differences among the three groups at baseline. $P < .05$ was considered statistically significant.

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dose DRP-OC–containing preparation administered to hirsute women with PCOS, alone or in combination with metformin or CPA, affects some cardiovascular risk factors.

MATERIALS AND METHODS

Study Population

The study protocol was approved by the institutional review board of the University of Pisa. Informed consent was obtained from all participants and/or their parents before entering in the study.

Forty-eight consecutive patients with PCOS who attended to the Outpatient Clinic of Reproductive Endocrinology of the University of Pisa were enrolled prospectively for the study during 2008 (from March to November). The mean age was 24 years (range, 15–34 years). Women were diagnosed with PCOS on the basis of the presence of chronic oligomenorrhea and hirsutism, according to the Rotterdam (23) and National Institutes of Health criteria (24). Hirsutism was defined as a Ferriman-Gallwey score >8. The hirsutism score in these women ranged from 9 to 22. Thirty-one women had polycystic ovaries on ultrasound examination. Subjects with body mass index (BMI) >30 kg/m^2 and those with a gynecologic age less than 2 years after menarche or aged >35 years at the time of evaluation were excluded. None of the patients were affected by hypertension, glucose intolerance, or diabetes mellitus, and none of the subjects had a personal history of cardiovascular events or received treatment with OCs, antiandrogens, insulin sensitizers, or drugs that might interfere with blood pressure regulation, lipid profile, or carbohydrate metabolism for the previous 6 months.

Subjects with hyperprolactinemia, hypo- or hyperthyroidism, congenital adrenal hyperplasia, Cushing's syndrome, or androgen-secreting tumors were excluded from this study.

Study Design

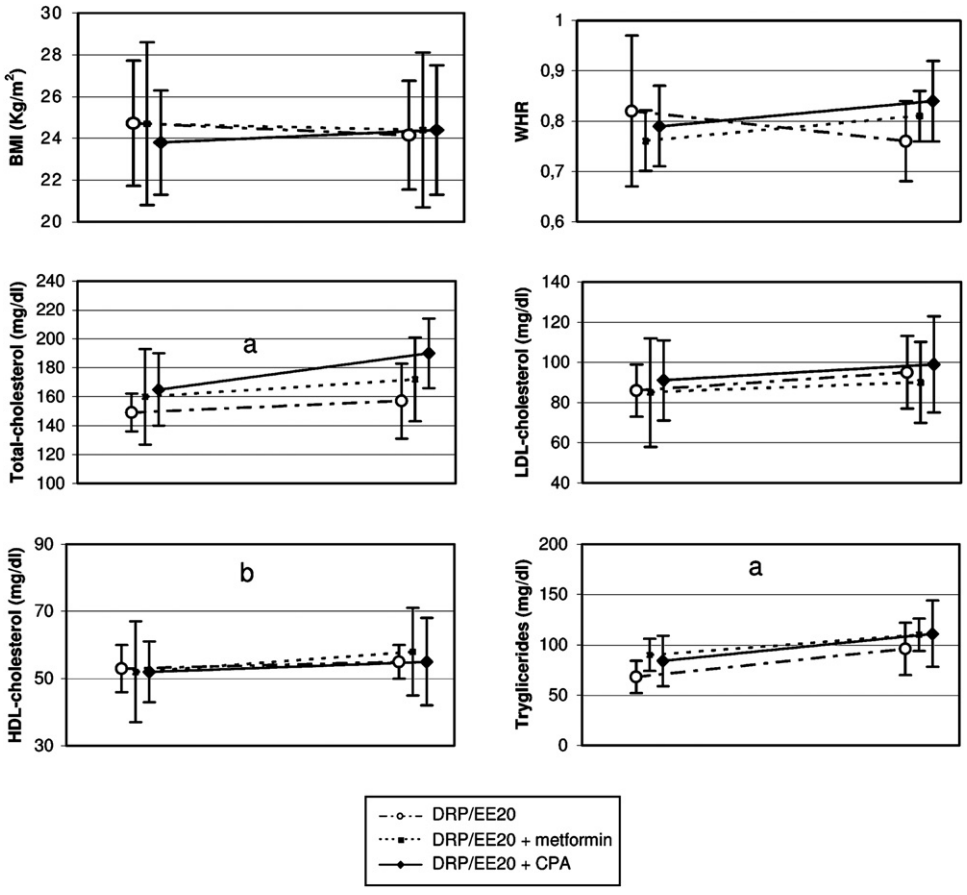
Subjects were randomized to receive an antiandrogenic low-dose OC pill in cycles of 28 days (21 pills containing 20 μg EE plus 3 mg of DRP [DRP/EE20], followed by 7 no-pill days; Yasminelle; Bayer Schering Pharma, Milan, Italy) alone (16 subjects), or the same estro-progestin preparation combined with 500 mg of metformin (Glucophage; Merck, Florence, Italy) three times daily (16 subjects). A third group (16 subjects) received the same low-dose pill plus 12.5 mg/d of CPA (Androcur; Bayer Schering Pharma). Because CPA is stored in the adipose tissue during the period of administration, the drug was administered during the first 10 days of the estro-progestin preparation. The allocation sequence of the treatments was decided by a third party (D.P.) before the recruitment of patients by random-number tables. Treatments were started the first day of a spontaneous or induced menstrual cycle. Metformin was started at a 750-mg dose daily during the first week of treatment, with the aim of minimizing gastrointestinal side effects. All patients were instructed to not modify their diet and physical activity throughout the trial. All women received their medications for 6 months.

All subjects were studied at baseline, during the follicular phase of the menstrual cycle (3–7 days after the onset of last spontaneous or progestin-induced menstrual bleeding), and after six cycles of treatment (1 out of the last 4 days of the 21-pill intake regimen). Height and weight were measured on the morning of testing, and BMI was calculated. Waist and hip circumferences were measured, and waist/hip ratio (WHR) was calculated. Diastolic and systolic blood pressure was also measured in each woman. Blood pressure was measured by the same trained physician using a standard mercury sphygmomanometer with an appropriate cuff size. Blood samples were obtained between 8:00 AM and 8:30 AM after an overnight fast for determination of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations. An oral glucose tolerance test (OGTT) was also performed. Plasma samples for glucose and insulin concentrations were collected before and after 30, 60, 90, and 120 minutes from a 75-g oral glucose administration. Blood samples for determination of total T, androstenedione (A), and SHBG concentrations were also obtained. The free androgen index (FAI) was calculated: T (nmol/L)/SHBG (nmol/L) × 100.

Insulin plasma levels were expressed as area under the curve after glucose ingestion (AUC-insulin). The AUC was calculated by trapezoidal rule and expressed as micro-units per milliliter × 120 minutes. As for indicators of insulin sensitivity, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: [blood glucose (nmol/L) × insulin (μU/mL)]/22.5. The glucose/insulin ratio (G/I) was also calculated.

FIGURE 1

Changes in clinical characteristics and in the lipid profile of patients with PCOS submitted to treatment with DRP/EE20 alone or combined with metformin or CPA for 6 months. Data are expressed as means ± SD. The Wilcoxon test was performed to evaluate the differences in the response to each treatment in each group. $P<.05$ was considered statistically significant. [a]$P<.01$ vs. baseline value in the DRP/EE20 plus CPA group; [b]$P<.05$ vs. baseline value in the DRP/EE20 plus metformin group.



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Laboratory Analysis

Total cholesterol, HDL cholesterol, and triglycerides were determined by enzymatic methods (Beckman Coulter, Galway, Ireland). Low-density lipoprotein cholesterol was calculated using Friedewald's equation ([total - cholesterol - HDL] - [tryglicerides/5]). Insulin was determined by an immunoradiometric assay (DiaSorin, Vercelli, Italy); the intra-assay and interassay coefficients of variation (CVs) for insulin assay were 2.1%–2.6% and 2.9%–4.7%, respectively. Blood glucose was determined using the glucose oxidase method.

Androstenedione concentrations were determined by RIA (Biosource Europe, Nivelles, Belgium). The intra-assay and interassay CVs for A assay were 3.2%–4.5% and 5.9%–9.0%, respectively. Total T concentrations were determined by RIA (Ortho-Clinical Diagnostic, S.J. dos Campos, Brazil). The intra-assay and interassay CVs of total T were 2.3%–3.1% and 4.9%–7%, respectively.

Statistical Analyses

Assuming that, in the comparison of the differences between the means of paired data, the difference induced by treatment was equal to 1 SD of the difference and by setting type 1 error at 0.05 and type 2 error at 0.20, at least 10 subjects were sufficient in each group to detect statistically significant modification in the data analyzed. For statistical analysis, because of the variability for some of the parameters tested, nonparametric tests have been used. The differences among the three groups at baseline and at the end of treatment were analyzed by the Kruskal-Wallis test. To evaluate the differences in response to each treatment in each group, the Wilcoxon test was used. All data are reported as mean ± SD. For all analysis a P value of $<.05$ was considered statistically significant.

RESULTS

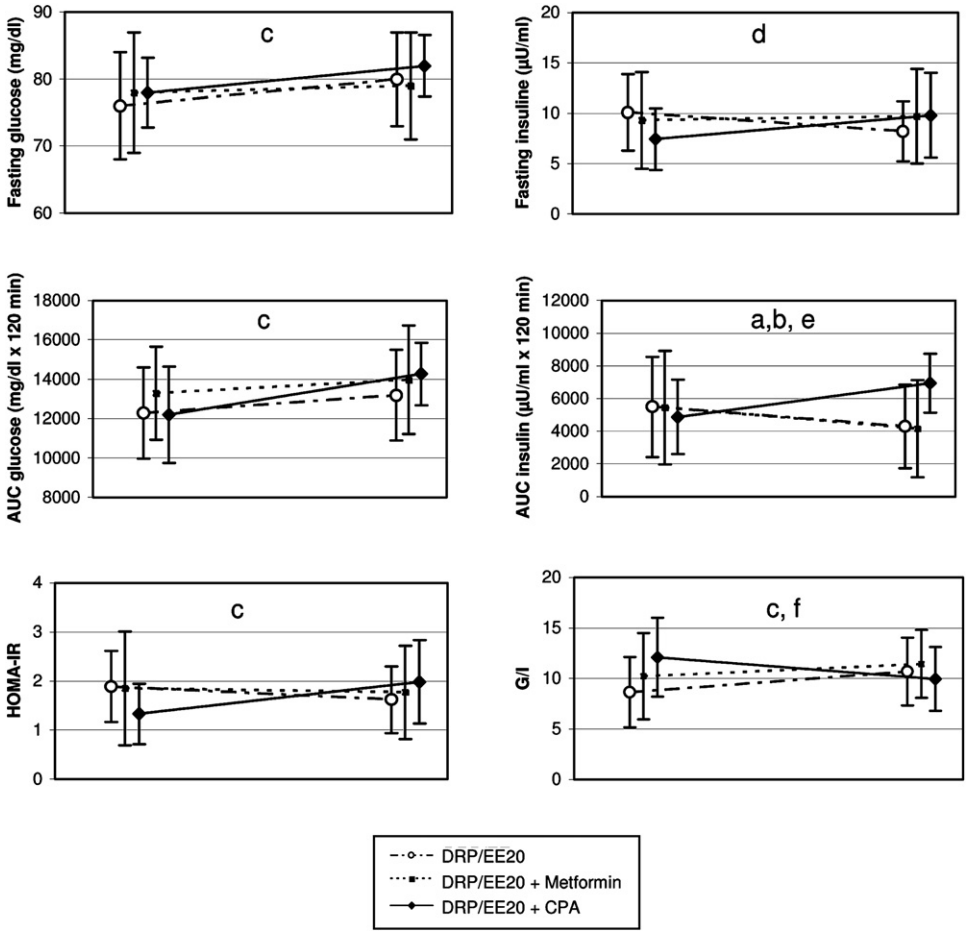
Among the enrolled women, 25% had hyperandrogenemia (defined as total T >0.8 ng/mL and/or A >3.1 ng/mL). At baseline no subject had glucose intolerance. Insulin resistance was found in 20% of enrolled women and dyslipidemia in 38%. The baseline characteristics of each group are summarized in Table 1 and show no differences among the patients randomized to each treatment. All but 1 patient completed the study. This subject, enrolled in the DRP/EE20 + metformin group, interrupted the study because of gastrointestinal side effects.

Effects of Treatment on Clinical Characteristics and Lipid Profile

The BMI and WHR were not modified by any pharmacologic approach (Fig. 1). No changes in diastolic and systolic blood pressure were observed. In the DRP/EE20 group no significant changes in lipid

FIGURE 2

Changes in index of glucose tolerance and insulin sensitivity in patients with PCOS treated with DRP/EE20 alone or combined with metformin or CPA for 6 months. Data are expressed as means ± SD. The Wilcoxon test was performed to evaluate the differences in the response to each treatment in each group. $P<.05$ was considered statistically significant. [a]$P<.01$ vs. baseline value in the DRP/EE20 + CPA group; [b]$P<.05$ vs. baseline value in the DRP/EE20 + metformin group; [c]$P<.005$ vs. baseline value in the DRP/EE20 + CPA group; [d]$P<.001$ vs. baseline value in the DRP/EE20 + CPA group; [e]$P<.05$ vs. baseline value in the DRP/EE20 group; [f]$P<.01$ vs. baseline value in the DRP/EE20 group. AUC = AUC during OGTT.



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profile were observed (Fig. 1). In women treated with DRP/EE20 + metformin, the HDL cholesterol concentrations only increased significantly ($P<.05$) when compared with baseline values (Fig. 1).

In women treated with DRP/EE20 + CPA a significant increase ($P<.01$) in total cholesterol and triglyceride levels was observed, whereas HDL and LDL cholesterol levels did not change during the study (Fig. 1). At the end of treatment total cholesterol levels in the DRP/EE20 + CPA group were significantly higher ($P<.001$) than in the other groups.

Effects of Treatment on Glucose Tolerance and Insulin Sensitivity

Fasting and stimulated glucose levels did not change compared with baseline values in the DRP/EE20 and DRP/EE20 + metformin groups. Conversely, both fasting and stimulated glucose levels were significantly increased ($P<.005$) in DRP/EE20 + CPA–treated women without reaching pathologic values (Fig. 2). Fasting insulin levels did not change in the DRP/EE20 and DRP/EE20 + metformin groups. Conversely, fasting insulin significantly increased ($P<.001$) in women treated with DRP/EE20 + CPA compared with baseline (Fig. 2). The AUC for insulin statistically decreased in the DRP/EE20 and DRP/EE20 + metformin groups ($P<.05$), but the AUC for insulin significantly increased in the DRP/EE20 + CPA group ($P<.01$) (Fig. 2).

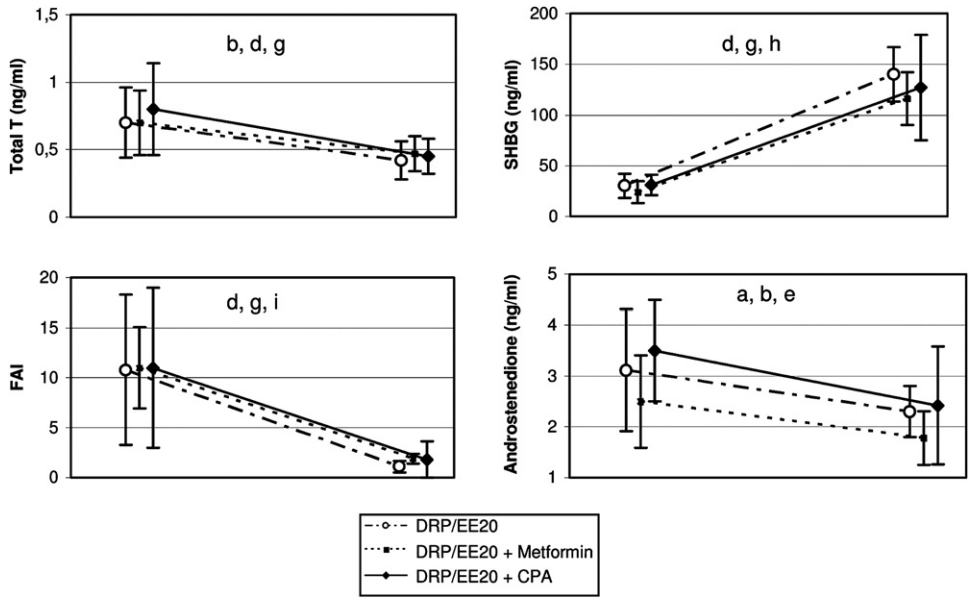
Indexes of insulin sensitivity improved in patients with PCOS treated with DRP/EE20 and with DRP/EE20 + metformin, and they worsened in the DRP/EE20 + CPA group (Fig. 2). The HOMA-IR index slightly decreased in the DRP/EE20 and DRP/EE20 + metformin groups without reaching statistical significance, whereas this index significantly increased in the DRP/EE20 + CPA group ($P<.005$) (Fig. 2). The G/I index increased significantly in women treated with DRP/EE20 ($P<.01$), and it decreased significantly in those treated with DRP/EE20 + CPA ($P<.005$).

Effects of Treatment on Serum Androgen Levels

All groups showed a significant decrease in total T levels compared with baseline ($P<.001$ for DRP/EE20 and DRP/EE20 + CPA;

FIGURE 3

Changes in serum androgen profile of patients with PCOS treated with DRP/EE20 alone or combined with metformin or CPA for 6 months. Data are expressed as means ± SD. The Wilcoxon test was performed to evaluate the differences in the response to each treatment in each group. $P<.05$ was considered statistically significant. [a]$P<.01$ vs. baseline value in the DRP/EE20 + CPA group; [b]$P<.05$ vs. baseline value in the DRP/EE20 + metformin group; [c]$P<.005$ vs. baseline value in the DRP/EE20 + CPA group; [d]$P<.001$ vs. baseline value in the DRP/EE20 + CPA group; [e]$P<.05$ vs. baseline value in the DRP/EE20 group; [f]$P<.01$ vs. baseline value in the DRP/EE20 group; [g]$P<.001$ vs. baseline value in the DRP/EE20 group; [h]$P<.001$ vs. baseline value in the DRP/EE20 + metformin group.



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$P<.05$ for DRP/EE20 + metformin) (Fig. 3). The SHBG levels significantly increased in all groups ($P<.001$). As a consequence, the FAI was significantly reduced ($P<.001$) (Fig. 3).

Androstenedione levels were significantly reduced in all groups ($P<.05$ in the DRP/EE20 and DRP/EE20 + metformin groups; $P<.01$ in the DRP/EE20 + CPA group) (Fig. 3).

DISCUSSION

The present results show that DRP associated with 20 μg EE is safe in nonobese hirsute patients with PCOS, showing overall beneficial effects on the metabolic profile. The most interesting finding is the lack of a negative impact on carbohydrate metabolism. Conversely, an improvement in insulin sensitivity was observed, as documented by the decrease in basal insulin and in the insulin response to an oral glucose load, leading to an amelioration of the index of insulin sensitivity. No deleterious changes in lipid metabolism were observed. Previous results obtained in 15 hirsute patients with PCOS treated with DRP (3 mg) combined with a higher dose of EE (e.g., 30 μg) for 12 cycles showed that there was no negative impact on glycoinsulinemic homeostasis and a trend toward an improvement of lipid profile (22). These results suggest that the use of DRP can reduce the metabolic concerns that are specific to women with PCOS, regarding the possible use of OCs in these women. Oral contraceptives containing 30 μg or more of EE associated with second-generation progestins, such as levonorgestrel, decrease peripheral insulin receptors (25) and induce subclinical abnormalities in carbohydrate metabolism (26, 27). Oral contraceptives with third-generation progestins (desogestrel and gestodene, norgestimate) are considered more neutral (28–30), but in some studies a decrease in insulin sensitivity has been reported (31–33). The androgenic properties of all 19 nortestosterone derivatives may play a role in reducing insulin sensitivity (20, 34). No negative changes or an improvement in insulin sensitivity with progestins with antiandrogenic activity have been documented by some investigators (31, 33). Drospirenone is a unique progestin, being related to 17α-spironolactone rather than derived from 19-nortestosterone. It exhibits both antimineralcorticoid and antiandrogenic activity (20). The antiandrogenic activity might explain the effect on insulin sensitivity. However, the antimineralcorticoid activity could also contribute to this effect. In fact, aldosterone induces insulin resistance through an inhibition of the biosynthesis and affinity of insulin receptors (35, 36). Drospirenone is the only progestin with aldosterone antagonist activity (20). On the basis of these data, it could be hypothesized that the improvement of insulin sensitivity observed in our study might be ascribed at least in part to the DRP–aldosterone antagonist activity per se. The lack of changes in body weight seems to exclude that a decrease in body weight explains our results. The addition of metformin to DRP does not modify the effects on insulin metabolism described in the group receiving only the pill. An increase in HDL cholesterol alone has been observed. In other words, metformin clearly does not outperform DRP/EE20 alone in improving insulin sensitivity. These observations further reinforce the contention that this combination is safe in terms of metabolic risk factors for cardiovascular disease. In contrast, the addition of CPA to DRP/EE20 completely abolishes these positive metabolic effects. In fact, the association of 12.5 mg/d CPA with DRP/EE20 decreases insulin sensitivity and glucose tolerance, along with an increase in triglyceride and total cholesterol levels. Different studies reported conflicting results on insulin sensitivity

in women with PCOS treated with EE plus CPA (14, 33, 37, 38). In studies involving 2 mg CPA, no changes in insulin concentrations and sensitivity or an improvement of insulin sensitivity has been reported in nonobese women with PCOS. A significant worsening of glucose tolerance has been reported with the same dose of CPA in obese insulin-resistant women with PCOS (38). A decrease in glucose uptake in peripheral tissues and an increase in insulin has been reported by Dahlgren et al. (37) with 100 mg CPA. Taken together, these results could suggest that although low doses of CPA are safe at least in nonobese women with PCOS, the use of high doses (12.5 mg in our study and 100 mg in Dahlgreen's study) may reduce insulin sensitivity. The use of more appropriate investigations of insulin sensitivity and larger studies are needed to validate our preliminary results.

In conclusion, the results of the present study do not support a harmful effect of all OCs in women with PCOS. In particular the present data show that in nonobese women with PCOS, DRP plus 20 mg EE improves the metabolic profile of these women—an effect that was not further improved with metformin supplementation. Conversely, the addition of high doses of CPA deteriorates insulin and glucose metabolism, making its use unfavorable in hirsute women with PCOS. Further research is needed to evaluate if these results may be extended to obese women with PCOS with severe metabolic derangement.

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