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HIRSUTISM

Comparison of two oral contraceptives containing either drospirenone or cyproterone acetate in the treatment of hirsutism

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Abstract

Combined oral contraceptives (COCs) are considered the first-line treatment for women with hirsutism. They diminish androgen release from the ovary and decrease plasma free testosterone levels by increasing sex hormone-binding globulin (SHBG) concentrations. COCs containing cyproterone acetate (CPA) and drospirenone (DRSP) have been proved effective for the treatment of acne and facial hirsutism. This study prospectively compared the clinical and biochemical efficacy of 3 mg DRSP/30 μg ethinyl estradiol (EE) and 2 mg CPA/35 μg EE combinations in a total of 91 patients with hirsutism. Individuals randomly received a cyclic combination of either DRSP/EE ($n = 48$) or CPA/EE ($n = 43$) for 12 months. Basal serum total testosterone, free testosterone, androstenedione, dehydroepiandrosterone sulfate and SHBG levels, as well as Ferriman–Gallwey scores, were determined before and after treatment. Both COCs achieved a similar effect on clinical hirsutism scores, in addition to serum androgen and SHBG levels, after completion of therapy. The percentage reductions in total hirsutism score (median % (min–max)) during therapy were 0.70 (0–0.58) vs. 0.57 (0.10–1.00) at 6 months ($p = 0.028$) and 0.80 (0–0.42) vs. 0.81 (0–0.75) at 12 months ($p = 0.6$) in the DRSP/EE and CPA/EE groups, respectively. In conclusion, the DRSP/EE combination is at least as effective as the CPA/EE combination in improving hirsutism scores.

Keywords: *Drospirenone, cyproterone acetate, oral contraceptive, hirsutism, hyperandrogenism, ethinyl estradiol*

Introduction

Combined oral contraceptives (COCs) effectively suppress ovarian androgen production, and form the first step in the traditional treatment of women with hirsutism [1]. Their progestational activity lowers luteinizing hormone (LH) secretion and hence the release of LH-mediated ovarian androgen. The beneficial effect of the estrogenic component is mainly attributable to its sex hormone-binding globulin (SHBG) elevating ability, which decreases the amount of free testosterone (T) available [2]. However, the increase in plasma SHBG concentration is blunted by the androgenic activity of the progestin. Therefore it is preferable, but not critical, to select a COC containing a progestin with low androgenic activity [3].

Cyproterone acetate (CPA) is known to be a potent progestin with strong antiandrogenic activity at target sites [3]. In hirsute women, it attenuates androgen action by receptor blockage and by inducing hepatic T clearance [4]. Although CPA may be used alone at daily doses of 50–100 mg during the first 10 days of the cycle, it is generally used in conjunction with oral ethinyl estradiol (EE). The combination of daily 2 mg CPA with 35 μg EE has proved to be effective in the treatment of hirsutism [5,6]. Higher doses of CPA are recommended in cases with moderate to severe hirsutism or when a more rapid response is desired [4,7]. Nevertheless, clinical improvement over 12 months is comparable with high (i.e. 20–100 mg) and low (i.e. 2 mg) daily doses of CPA [5].

The new progestin drospirenone (DRSP) is a spironolactone analog which has antimineralocorticoid and antiandrogenic activity. Its pharmacological and biochemical profiles are similar to those of endogenous progesterone. An important feature of DRSP is that it does not attenuate the EE-induced increase in SHBG; neither does it interfere with androgen binding to SHBG [8]. DRSP counteracts the estrogen-induced stimulation of the renin–angiotensin system and therefore has the potential to reduce the

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uncommon side-effects of estrogen on blood pressure and body weight. Other benefits of DRSP include improvement in acne and other skin-related problems, which are in part related to its antiandrogenic activity [9].

Since recent studies have shown that DRSP/EE is effective against acne and seborrhea, attention has focused on whether it will also improve hirsutism. Initial studies on patients with polycystic ovary syndrome (PCOS) were promising [10]. Recently, we have shown that a cyclic combination of 3 mg DRSP and 30 μg EE daily achieved a significant improvement in hair growth in patients with moderate to severe hirsutism over 12 months [11]. Some of those patients were also included in the present study, where our aim was to compare the clinical and biochemical efficacy of 3 mg DRSP/30 μg EE with that of 2 mg CPA/35 μg EE on hirsutism.

Patients and methods

Patients

This prospective randomized study was initially conducted on a population of 100 unselected women with moderate to severe hirsutism. All were recruited from our outpatient hirsutism clinic after written informed consent was given. The Institutional Ethics Committee of Erciyes University School of Medicine approved the study. Eligible participants were non-pregnant premenopausal women with no evidence of androgen-secreting adrenal or ovarian neoplasm (total plasma T <200 ng/dl, plasma dehydroepiandrosterone sulfate (DHEAS) <7000 ng/ml), Cushing's syndrome, or congenital adrenal hyperplasia (early follicular-phase plasma 17-hydroxyprogesterone <3 ng/ml). Each patient underwent a complete medical examination, as well as an endocrine profile (thyroid-stimulating hormone, free thyroxine and prolactin) and hepatic and renal function analysis. Those who were on COCs or long-acting progestins during the 6 months before enrollment were excluded.

The degree of hirsutism was graded according to the modified Ferriman–Gallwey (FG) scoring system [12] and patients with FG score ≥ 8 were included in the study. No patient had any sign of virilization. The same physician (I.I.M.), blinded to the treatment regimen, assessed all patients to eliminate the inter-observer variability. All cases were requested not to epilate for at least one month before each evaluation.

The diagnosis of PCOS was based on the presence of at least one ovary with typical polycystic features (i.e. eight or more peripherally arranged discrete follicles measuring 2–9 mm in diameter with or without an enlarged hyperechogenic central stroma) and/or an enlarged ovarian volume (i.e. >10 ml), in addition to the clinical signs of hyperandrogenism [13,14].

Patients were randomly assigned to a daily dose of 3 mg DRSP/30 μg EE (Yasmin®; Schering AG, Berlin, Germany) (group 1; $n=50$) or 2 mg CPA/35 μg EE (Diane® 35; Schering AG) (group 2; $n=50$), according to a computer-based randomization sequence. Patients were not blinded to therapy. They were told to take the medication for 21 days, followed by a 7-day pill-free period. Clinical and hormonal responses were evaluated at 6 and 12 months after therapy was started. Because a total of nine patients were lost to follow-up or became pregnant, 91 patients (48 in group 1 and 43 in group 2) completed the treatment period and this paper presents their results. The number of patients with PCOS in group 1 and 2 was 35 and 30, respectively. The remaining 26 patients had idiopathic hirsutism (13 patients each in group 1 and group 2).

Hormone assay

Before beginning treatment, venous serum samples for hormonal assay were taken after an overnight fast in the early follicular phase (in women with regular menstrual cycles) or on a convenient day for those who were amenorrheic. Sampling was repeated and in addition renal and hepatic functions were checked after 6 and 12 months of therapy. All blood specimens were stored at -20°C until assayed.

Serum total T (DSL-4000; Diagnostic Systems Laboratories, Webster, TX, USA), free T (DSL-4900; Diagnostic Systems Laboratories), androstenedione (A) (DSL-4000; Diagnostic Systems Laboratories) and DHEAS (Immunotech, Marseilles, France) were measured by radioimmunoassay, and SHBG was measured by immunoradiometric assay (Orion Diagnostica, Espoo, Finland), using commercial kits. The intra-assay and inter-assay coefficient of variation were respectively 8.1 and 9.1% for total T, 3.7 and 7.9% for free T, 4.3 and 6.0% for A, 5.6 and 4.1% for DHEAS, and 4.0 and 5.5% for SHBG.

Statistical analysis

All datasets were subjected to normality testing using the Kolmogorov–Smirnov method and data are reported as either mean $\pm$ standard error (SE) (for normally distributed data) or as median with range (for skewed data). Continuous variables were analyzed with parametric or non-parametric methods according to whether they showed normal distribution or not. Changes in serum hormone levels between baseline and 6 and 12 months of therapy with DRSP/EE or CPA/EE were analyzed by two-way analysis of variance for repeated measures and adjustment for multiple comparisons was performed with the Bonferroni correction. The change in hirsutism score within the same group and between

groups was compared with the Friedman test (multiple comparisons were carried out with Dunn's test) and the Mann–Whitney *U* test, respectively. Percentage reductions of hirsutism score are reported as mean ± SE. Independent proportions and medians between groups were compared with the χ^2 and Mann–Whitney *U* test, respectively. A p value of <0.05 was regarded as statistically significant. Analysis was performed with the Statistical Package for the Social Sciences version 11.0 (SPSS Inc., Chicago, IL, USA).

Results

The median age and body mass index plus the number of patients with polycystic ovaries, PCOS, menstrual abnormalities and obesity were similar in both treatment groups (Table I). The baseline serum SHBG, total T, free T and A levels of patients with and without PCOS were comparable, whereas the serum DHEAS level of patients with PCOS was significantly lower than that of patients without PCOS (Table II).

Changes in serum hormone levels during therapy are summarized in Table III. Both treatment groups had similar basal serum androgen and SHBG levels.

Table I. Characteristics of women in both groups.

	Group 1 (DRSP/EE) ($n=48$)	Group 2 (CPA/EE) ($n=43$)	p
BMI (kg/m^2)	23 (16–38)	21 (15–39)	>0.05
Age (years)	25 (18–35)	23 (18–45)	>0.05
Oligo-/amenorrhea	25 (52.1)	26 (60.5)	>0.05
Obese	12 (25)	5 (11.6)	>0.05
Polycystic ovaries	30 (62.5)	27 (62.8)	>0.05
PCOS	35	30	>0.05

DRSP, drospirenone; EE, ethinyl estradiol; CPA, cyproterone acetate; BMI, body mass index; PCOS, polycystic ovary syndrome; data are expressed as *n* (%) or median (min–max).

Table II. Basal serum hormone levels in hirsute women with and without PCOS.

	Hirsute women ($n=91$)		
	With PCOS ($n=65$)	Without PCOS ($n=26$)	p
SHBG (nmol/l)	38.1 ± 1.9	37.9 ± 2.5	0.95
Total T (ng/dl)	84.0 ± 4.1	88.8 ± 5.9	0.51
Free T (pg/ml)	2.2 ± 0.2	2.3 ± 0.2	0.64
A (ng/ml)	2.5 ± 0.1	2.8 ± 0.2	0.10
DHEAS (μg/ml)	2.2 ± 0.1	2.9 ± 0.3	0.01

SHBG, sex hormone-binding globulin; T, testosterone; A, androstenedione; DHEAS, dehydroepiandrosterone sulfate; data are expressed as mean ± standard error.

There was a significant increase in serum SHBG and a significant decrease in serum total T, free T and A during the treatment period in groups 1 and 2. Improvement in serum androgen levels was comparable for both regimens after 6 and 12 months of therapy. There was no significant change in serum DHEAS levels in both groups during therapy.

Before beginning therapy the total hirsutism score was similar in both groups (Mann–Whitney *U* test; $p > 0.05$) (Table IV). Hair growth among different body parts was also comparable in both groups ($p > 0.05$), except for a significantly more intense pre-treatment hair texture over the chest and back region of patients in the CPA/EE group ($p < 0.05$).

Both regimens achieved a statistically significant decrease in total hirsutism score, as well as a significant decrease in hair growth in all body parts after 6 and 12 months of therapy, when compared with baseline values (Friedman non-parametric test; $p < 0.001$) (Table IV). The percentage reductions in total hirsutism scores (median % (min–max)) during therapy were 0.70 (0–0.58) vs. 0.57 (0.10–1.00) at 6 months ($p = 0.028$) and 0.80 (0–0.42) vs. 0.81 (0–0.75) at 12 months ($p = 0.6$) in the DRSP/EE and CPA/EE groups, respectively (Figure 1). Diminished hair growth was more evident after 6 months on the chest, waist, thigh and arm region with the DRSP/EE regimen (Mann–Whitney *U* test; $p < 0.05$) (Figure 2).

Both regimens achieved good cycle control without serious side-effects necessitating cessation of therapy. Five (10.4%) patients in the DRSP/EE group and eight (18.6%) patients in the CPA/EE group reported inter-menstrual spotting during the first 3 months, which resolved spontaneously without requiring intervention. Common side-effects of COCs, such as mild headache, breast tenderness and weight gain, were reported less often by patients treated with DRSP/EE than by patients treated with CPA/EE (data not shown).

Discussion

This study showed that the cyclic administration of 30 μg EE plus 3 mg DRSP and 35 μg EE plus 2 mg CPA combination for 21 days followed by a 7-day pill-free interval provided similar improvement in body hair growth and were both well tolerated, without causing serious side-effects. The decrease in total FG score was slightly faster in patients treated with DRSP/EE, whereas both combinations showed similar amelioration of facial hirsutism. Our findings support those of Ibanez and de Zegher [15], who recently reported that 30 μg EE plus 3 mg DRSP combination, with or without daily 62.5 mg flutamide plus 850 mg metformin, reduced the FG score significantly after 9 months of therapy in patients with PCOS. Similarly, Guido and colleagues [10],

Table III. Serum hormone levels before and during treatment with DRSP/EE regimen ($n = 48$) and CPA/EE regimen ($n = 43$).

	Plasma hormone level at indicated month of treatment						
	Baseline	6 months	12 months	*F*	p^*	$p^\dagger$	$p^\ddagger$
SHBG (nmol/l)							
DRSP/EE	35.8 ± 2.3^a	45.4 ± 3.2^a	52.6 ± 4.4^c	34.7	<0.001	0.065	0.873
CPA/EE	40.7 ± 1.9^a	45.2 ± 2.1^{ab}	49.7 ± 2.2^b				
DHEAS (μg/ml)							
DRSP/EE	2.6 ± 0.2	2.6 ± 0.2	2.5 ± 0.2	4.99	0.008	0.894	0.018
CPA/EE	2.2 ± 0.1	2.0 ± 0.1	2.0 ± 0.1				
A (ng/ml)							
DRSP/EE	2.6 ± 0.1^a	2.4 ± 0.1^b	2.3 ± 0.1^b	20.5	<0.001	0.283	0.992
CPA/EE	2.7 ± 0.1^a	2.4 ± 0.1^b	2.2 ± 0.1^b				
Total T (ng/dl)							
DRSP/EE	88.7 ± 4.4^a	72.7 ± 3.8^b	69.7 ± 4.1^b	44.5	<0.001	0.607	0.227
CPA/EE	81.5 ± 5.1^a	68.4 ± 5.2^b	61.2 ± 3.8^b				
Free T (pg/ml)							
DRSP/EE	2.2 ± 0.2^a	1.9 ± 0.2^b	1.7 ± 0.1^b	16.1	<0.001	0.587	0.885
CPA/EE	2.2 ± 0.2^a	2.0 ± 0.1^{ab}	1.8 ± 0.1^b				

DRSP, drospirenone; EE, ethinyl estradiol; CPA, cyproterone acetate; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; A, androstenedione; T, testosterone; data expressed as mean $\pm$ standard error; analysis was carried out by two-way analysis of variance for repeated measures, groups with different superscript letters were found to have statistically significant differences; *test of within-subjects effects; †interaction between both regimens; ‡test of between-subjects effects.

Table IV. Hirsutism score of nine body parts before and during therapy with DRSP/EE regimen ($n = 48$) and CPA/EE regimen ($n = 43$).

	Hirsutism score at indicated month of treatment				
	Baseline	6 months	12 months	Friedman χ^2	p^*
Upper lip					
DRSP/EE	2 (0–4)	0 (0–3)	0 (0–2)	79.94	<0.001
CPA/EE	2 (0–4)	1 (0–2)	0 (0–2)	66.05	<0.001
Chin					
DRSP/EE	2 (0–4)	0 (0–3)	0 (0–2)	81.94	<0.001
CPA/EE	2 (0–4)	1 (0–4)	0 (0–2)	57.13	<0.001
Chest					
DRSP/EE	1 (0–4)	0 (0–2)	0 (0–2)	52.25	<0.001
CPA/EE	0 (0–4)	0 (0–2)	0 (0–1)	55.18	<0.001
Back					
DRSP/EE	1 (0–3)	0 (0–2)	0 (0–2)	32.72	<0.001
CPA/EE	1 (0–3)	1 (0–2)	1 (0–2)	48.87	<0.001
Waist					
DRSP/EE	1 (0–4)	0 (0–2)	1 (0–4)	63.38	<0.001
CPA/EE	2 (0–4)	1 (0–4)	0 (0–2)	59.40	<0.001
Thigh					
DRSP/EE	3 (1–4)	1 (0–2)	1 (0–2)	89.44	<0.001
CPA/EE	4 (0–4)	1 (0–4)	1 (0–3)	73.34	<0.001
Arm					
DRSP/EE	1 (0–3)	1 (0–2)	1 (0–2)	56.58	<0.001
CPA/EE	2 (0–3)	1 (0–2)	1 (0–2)	50.16	<0.001
Upper abdomen					
DRSP/EE	1 (0–4)	0 (0–2)	0 (0–1)	62.85	<0.001
CPA/EE	2 (0–4)	1 (0–2)	0 (0–2)	56.72	<0.001
Lower abdomen					
DRSP/EE	2 (0–4)	0.5 (0–2)	0 (0–2)	78.56	<0.001
CPA/EE	2 (0–4)	1 (0–3)	0 (0–2)	72.41	<0.001
Total					
DRSP/EE	15 (8–28)	5 (1–13)	3 (0–8)	40.19	<0.001
CPA/EE	16 (9–28)	7 (1–18)	4 (0–12)	81.59	<0.001

DRSP, drospirenone; EE, ethinyl estradiol; CPA, cyproterone acetate; data are expressed as median (min–max); *change within treatment groups (Friedman non-parametric test).

who investigated the long-term effect of DRSP/EE on clinical and endocrine-metabolic features in women affected by PCOS, found a significant change in the grade of hirsutism towards a lower level over 12 cycles of treatment.

COCs containing CPA as well as DRSP (i.e. Diane 35 and Yasmin, respectively) have been marketed for the treatment of acne and seborrhea. Diane 35 has also been used for the management of hirsutism. Although this drug contains a low dose of CPA, it is equally effective in ameliorating hirsutism after 1 year as higher doses of CPA [5]. Therefore, it has been suggested that the effects of CPA are predominantly mediated by its progestogenic action rather than antiandrogenic action [16]. Given that DRSP also exhibits a significant progestogenic activity and that the DRSP/EE combination is effective in treating patients with hirsutism [11], the purpose of the present study was to compare the efficacy of Yasmin and Diane 35 for the treatment of hirsutism.

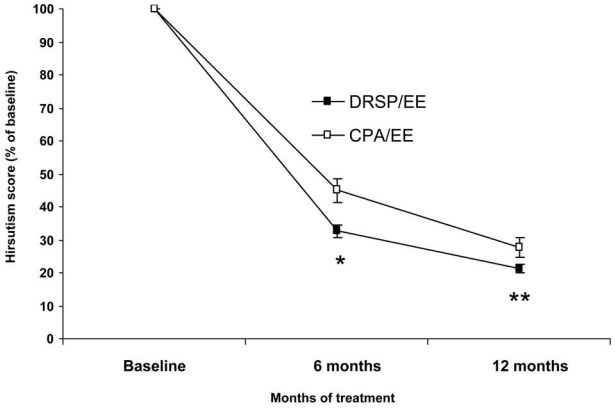

Figure 1. Change in hirsutism score during 12 months of treatment with drospirenone (DRSP)/ethinyl estradiol (EE) or cyproterone acetate (CPA)/EE. Values for hirsutism score are mean ± standard error, expressed as a percentage of the baseline (time 0) hirsutism score. DRSP/EE vs. CPA/EE at 6 months of therapy: $*p = 0.028$; DRSP/EE vs. CPA/EE at 12 months of therapy: $**p = 0.6$.

Both regimens achieved a similar improvement in endocrine response, which consisted of falls in serum A, total T and free T levels, and an increase in SHBG level. Other studies have shown similar changes in serum hormone levels with COC treatment [10,17–23]. Change in serum free T level is related to the decrease in total T and increase of serum SHBG concentration [24]. The former mechanism is common to all COCs and reflects the progestin-mediated suppression of gonadotropin release and subsequent reduction of ovarian androgen synthesis. The latter, however, is mainly attributable to the stimulation of hepatic SHBG synthesis, which is an effect of the estrogenic component of COCs. Hyperandrogenism itself, as well as progestins with androgenic activity, counteracts the beneficial effect of estrogen on serum SHBG concentration. Thus, treating hirsute patients with COCs containing high doses of estrogen together with progestins devoid of androgenic activity (i.e. CPA or DRSP) has much less of an effect on the SHBG concentration [8,10], and they should therefore be more effective for the treatment of hirsutism. A previous study has shown that COCs containing DRSP have a more profound effect on serum SHBG compared with those containing CPA [10]. Similar findings were not evident in the present study, as there was a more rapid but not statistically significant increase in SHBG over the first 6 months in patients who had received DRSP, compared with those who had received CPA. Nevertheless, this could explain why the clinical response was more rapid in patients who were prescribed the DRSP/EE combination. Further increase in SHBG

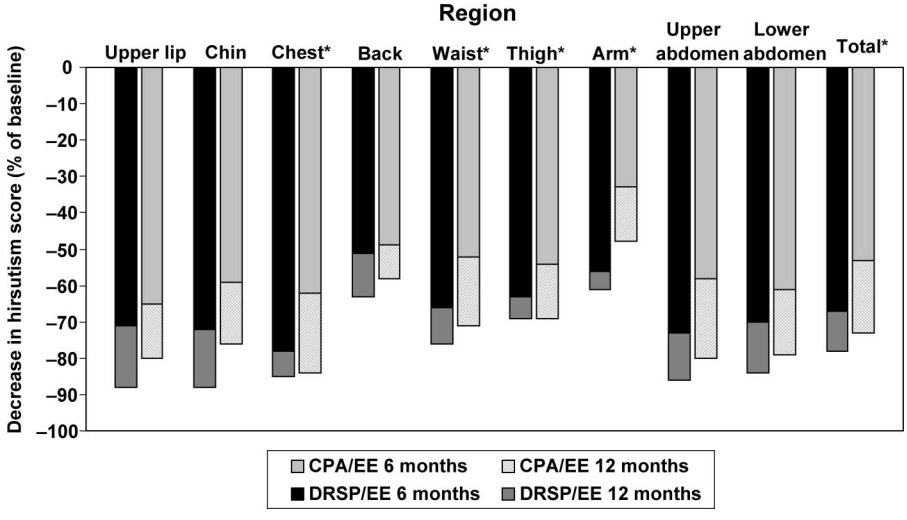

Figure 2. Change in hirsutism score during 12 months of therapy with drospirenone (DRSP)/ethinyl estradiol (EE) or cyproterone acetate (CPA)/EE. Values for hirsutism score are expressed as a percentage of the baseline (time 0) mean hirsutism score. DRSP/EE vs. CPA/EE at 6 months of therapy (Mann–Whitney non-parametric U test): $*p < 0.05$.

during the next 6 months was comparable in both treatment groups, as was the clinical improvement.

CPA and DRSP are capable of blocking peripheral androgen receptors at target organs [4,8], and CPA also increases the clearance of androgens by hepatic enzyme induction [25]. It has been claimed that these additional mechanisms of action may further potentate the antiandrogenic effect of these two progestins. However, it is questionable whether these features have any clinical significance in reversing androgenic signs, because animal studies have shown that a daily dose of 2 mg CPA does not have a noticeable antiandrogenic effect [18]. It has been suggested that it is the estrogenic effect on hepatic SHBG synthesis which is the predominant mechanism of action of COCs in controlling hirsutism [3,17,26]. The results of this study support this contention, as both regimens achieved a similar increase in serum SHBG concentration, and also improvement in the clinical signs of hirsutism. Usually, doses of estrogen required to achieve this effect are higher than those required for regular postmenopausal hormone therapy [3].

The decrease in serum DHEAS concentration should be the result of diminished adrenal androgen production, as only a small fraction of DHEAS in peripheral blood is of ovarian origin. Although various studies report an inhibition of adrenal androgen production in patients treated with COCs [18,27–29], this study did not show any change in serum DHEAS levels during CPA/EE or DRSP/EE therapy. Falsetti and Galbignani [17] reported a continuous decline of serum DHEAS levels in patients with PCOS treated with CPA/EE combination for 36 cycles. They emphasized that this finding could be attributed to the inhibitory effect of CPA on adrenal gland function, which has been observed in humans as well as in animals [30].

In this study, a substantial number of patients had PCOS because, besides hirsutism, their ovaries appeared polycystic on ultrasound [13,14]. Recent studies have raised concern regarding the issue that COCs may aggravate peripheral insulin resistance and exert other untoward metabolic actions that possibly enhance the long-term risk of diabetes mellitus and heart disease in patients with PCOS. One of those studies administered a desogestrel-containing pill [31], whereas others used a pill containing CPA that was administered to either obese [32] or lean [33,34] women with PCOS. Deterioration of glucose tolerance, as evidenced by higher plasma glucose levels during the oral glucose tolerance test with no change in plasma insulin concentrations, was evident in obese patients with PCOS [31,32]. However, two studies performed in lean patients with PCOS showed no change in glucose tolerance or insulin sensitivity after the administration of a COC containing CPA [33,34]. Although current data raises the issue that COCs may aggravate insulin resistance, further well-controlled studies are needed. Meanwhile, it seems prudent at the time of treatment to assess an individual woman with PCOS for risk factors for diabetes (e.g. positive family history, history of gestational diabetes). A logical approach to patients with PCOS may involve the measurement of peripheral insulin resistance and reserve COCs therapy to those with normal results.

We conclude that CPA- and DRSP-containing COCs have similar effects in patients with hirsutism, in terms of improving clinical hirsutism scores and serum androgen and SHBG levels. However, as COCs would be effective against excessive hair growth as long as the patient will take them, hypertension could become a major problem during long-term treatment. Here, the unique antimineralocorticoid activity of DRSP may be of advantage. Therefore, the DRSP/EE combination might be the preferable alternative if treatment with COCs is anticipated.

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