Efficacy of a new oral contraceptive containing drospirenone and ethinyl estradiol in the long-term treatment of hirsutism

Cem Batukan, M.D., and Iptisam Ipek Muderris, M.D.

Erciyes University, School of Medicine, Department of Obstetrics and Gynecology, Kayseri, Turkey

Objective: This study represents long term clinical and biochemical results and the response of different body parts to medical therapy with oral ethinyl estradiol/drospirenone combination in hirsute patients with or without polycystic ovary syndrom (PCOS).
Design: Prospective, open, controlled clinical study.
Setting: Outpatients at Erciyes University Medical School.
Patient(s): Fifty women with moderate to severe hirsutism were recruited. Two women were lost to follow-up.
Intervention(s): Women were treated with 3 mg of drospirenone and 30 μg of ethinyl estradiol for 12 cycles.
Main Outcome Measure(s): Hirsutism was assessed at 6-month intervals using the Ferriman-Gallwey (F-G) scoring system. Serum FSH, LH, total and free testosterone (T), androstenedione (A), dehydroepiandrosterone sulfate (DHEAS), estradiol (E_2), and sex-hormone binding globulin (SHBG) levels at 6 and 12 months of therapy were compared with baseline values.
Result(s): Total mean FG score declined by 67% and 78% after 6 and 12 months, respectively. Improvement was most prominent on the chest and abdomen, followed by the upper lip and chin. The lowest effect was observed on the back and arms. Serum levels of total and free T and A decreased, whereas SHBG levels increased significantly after 6 and 12 months when compared with baseline levels.
Conclusion(s): Drospirenone/ethinyl estradiol combination exerts significant antiandrogenic activity and is effective in improving facial hirsutism. The beneficial effect is most obvious after six cycles and continues thereafter at a slower rate. (Fertil Steril® 2006;85:436–40. ©2006 by American Society for Reproductive Medicine.)

Key Words: Yasmin®, drospirenone, hirsutism, oral contraceptive, hyperandrogenism

Combined oral contraceptives (COCs) effectively suppress ovarian androgen production and are now considered the first line treatment for women with hirsutism (1). Their progestational activity lowers luteinizing hormone (LH) secretion and thus LH-mediated ovarian androgen release. The beneficial effect of the estrogenic component is mainly attributable to its sex hormone-binding globuline (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 in the COC. Therefore, it is preferable, but not critical, to select a COC containing a progestine with low androgenic activity (3). Additional benefits of progestins are cycle control and resultant protection from endometrial hyperplasia.

The new progestin drospirenone (DRSP) is a spironolactone analogue that has antimineralocorticoid and antiandrogenic activity. Its pharmacological and biochemical profiles are similar to endogenous progesterone. An important feature of DRSP is that it neither attenuates the estrogen induced increase in SHBG, nor interferes with androgens from binding to SHBG (4). Further, DRSP has various favorable metabolic effects, including the potential to reduce blood pressure and body weight. In addition, DRSP is now incorporated in various hormone formulations, including the new monophasic COC Yasmin® (3 mg of DRSP and 30 μg of ethinyl estradiol [EE]; Schering AG, Berlin, Germany).

Despite the widespread use of daily oral EE/DRSP combination for contraception and recent introduction for acne and seborrhea (5, 6), its role in the treatment of patients with hirsutism needs to be determined. At present, evaluation of its efficacy has been limited to hirsute patients with polycystic ovary syndrome (PCOS) (7–9). The aim of this study was to represent our long-term clinical and biochemical results and expand experience with oral EE/DSPR combination therapy in hirsute patients with or without PCOS. In addition, for the first time, we have also accessed the response of different body parts to medical therapy with COCs.

MATERIALS AND METHODS

Patients

This prospective randomized study was conducted on a population of 50 unselected women with moderate to severe

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Reprint requests: Cem Batukan, M.D., Erciyes University Medical Faculty, Department of Obstetrics and Gynecology, Kayseri, Melikgazi 38039 Turkey (FAX: 00903524377614; E-mail: cbatukan@erciyes.edu.tr).

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hirsutism. All women were recruited from our Outpatient Hirsutism Clinic after informed consent was given. The University Ethics committee approved this study. Eligible participants were nonpregnant, premenopausal women with no evidence of androgen secreting adrenal or ovarian neoplasm (total plasma T <200 ng/dL; plasma dehydroepiandrosterone sulfate (DHEAS) <7,000 ng/mL), Cushing's syndrome, congenital adrenal hyperplasia (early follicular phase plasma 17-hydroxyprogesterone <3 ng/mL), or signs of virilization. In addition to the signs of hirsutism, patients with sonographically typical appearing ovaries (i.e., eight or more peripherally arranged discrete follicles with or without an enlarged hyperechogenic central stroma) were diagnosed with PCOS (10).

Thirty-eight (76%) patients were hyperandrogenic, having elevations of at least one serum androgen level over normal values (total T >80 ng/dL; free T >3.2 pg/mL; androstenedione (A) >2.7 ng/mL; DHEAS >3 μg/mL). Each patient underwent a complete medical examination, in addition to an endocrine profile, and hepatic and renal function analyses. Those who were taking any medication, including COC or long-acting progestines during the last 12 months before enrollment, were excluded.

To avoid interobserver errors, the same physician (I.I.M.) graded the degree of hirsutism according to the modified Ferriman-Gallwey (F-G) scoring system throughout the study (11). Because this study was conducted as part of a randomized trail, the observer was blinded to the treatment. Patients were requested not to epilate at least 1 month before each evaluation. Nine body areas were evaluated for density and area of hair growth, and quantified on a 0 (no hirsutism) to 4 (severe) point scale. Those who initially scored a total of ≥8 were included in the study. Patients were given a daily oral 30 μg of EE plus 3 mg of DRSP combination (Yasmin®, Schering AG, Berlin, Germany) through days 5–25 of the menstrual cycle for 12 months.

Serum samples for hormone analysis were taken before therapy at the early follicular phase (in women with regular menstrual cycles) or on a convenient day for those who were amenorrheic. Blood samples were collected after 6 and 12 months of treatment, at which time the hirsutism score was reevaluated. All sera were stored at −70°C until assayed.

Hormone Assay

Serum follicle stimulating hormone (FSH), luteinizing hormone (LH), total T, free T, A, estradiol (E_2) (DSL-4900, Webster, Texas) and DHEAS (Immunotech, Marseilles, France) were measured by radioimmunoassay; SHBG was measured by immunoradiometric assay (Orion Diagnostica, Espoo, Finland), using commercial kits. The intraassay and interassay coefficients of variation were 3.2% and 8.4% for FSH, 6.8% and 7.9% for LH, 8.1% and 9.1% for total T, 3.7% and 7.9% for free T, 4.3% and 6.0% for A, 5.2% and 5.5% for E_2, 5.6% and 4.1% for DHEAS, and 4.0% and 5.5% for SHBG.

Statistical Analysis

The values for serum hormone levels were expressed as means ± SD; hirsutism scores were expressed as medians (min-max). Serum hormone levels and hirsutism scores were compared longitudinally over time by one-way repeated measures analysis of variance. Statistical significance was set at $P<.05$. All analyses were performed using the statistical package for social science (SPSS), version 10.0 (SPSS Inc., Chicago, Illinois).

TABLE 1

Total and regional hirsutism score of different body parts before and after therapy with oral EE/DRSP.

	Hirsutism score			
Region	Basal	6 months	12 months	*P* value
Upper lip	2 (0–4)	0 (0–3)	0 (0–2)	<.001
Chin	2 (0–4)	0 (0–3)	0 (0–2)	<.001
Chest	1 (0–4)	0 (0–2)	0 (0–2)	<.001
Back	1 (0–3)	0 (0–2)	0 (0–2)	<.001
Waist	1 (0–4)	0 (0–2)	0 (0–2)	<.001
Thigh	3 (1–4)	1 (0–2)	1 (0–2)	<.001
Arm	1 (0–3)	1 (0–2)	1 (0–2)	<.001
Upper abdomen	1 (0–4)	0 (0–2)	0 (0–1)	<.001
Lower abdomen	2 (0–4)	0.5 (0–2)	0 (0–2)	<.001
Total	15 (8–28)	5 (1–13)	3 (0–8)	<.001

Note: Values are expressed as median (min–max). EE/DRSP = ethinyl estradiol/drospirenone.

Batukan. The effect of Yasmin® in hirsutism. Fertil Steril 2006.

TABLE 2

Changes of mean hirsutism score over 12 months.

	Decrease in mean hirsutism score (%)	
	6 months	12 months
Upper lip	−71	−88
Chin	−72	−88
Chest	−78	−85
Back	−51	−63
Waist	−66	−76
Thigh	−63	−69
Arm	−56	−61
Upper abdomen	−73	−86
Lower abdomen	−70	−84
Total	−67	−78

Note: Changes are expressed as percentage (%) of the baseline (time 0) mean hirsutism score.

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RESULTS

Because 2 women were lost to follow-up, 48 women completed the study, and their results are represented here. All individuals tolerated the treatment well without serious complaints or side effects necessitating discontinuation of therapy. Basal body mass index (BMI) and age of the patients were 25.7 ± 5.2 kg/m^2 and 24.6 ± 6.2 years, respectively. Twelve women were obese (BMI ≥30kg/m^2), and 25 reported oligo- or amenorrhea. Sonographically, the ovaries appeared polycystic in 30 patients.

Serious complications did not occur during therapy, and no individual complained of major side effects necessitating discontinuing of treatment. Intermenstrual bleeding (n = 5), breast tenderness (n = 2), and mild headache (n = 2) were well tolerated. Cycle control was acceptable, and no patient reported significant weight change.

Table 1 summarizes the effect of oral EE/DRSP combination on hirsutism scores of different body parts. The F-G score decreased significantly after 6 cycles, with a significant trend of amelioration being maintained at the end of 12 months. The total mean F-G score declined by 67% and 78% after 6 and 12 months, respectively. Improvement was most prominent on the chest and abdomen, followed by the upper lip and chin. The lowest effect was observed on the back and arms (Table 2).

Table 3 represents the endocrine changes during the treatment period. Serum LH, FSH, E_2, and DHEAS levels did not change during therapy, whereas total and free T and A levels decreased significantly. The SHBG levels increased significantly at 6 and 12 months when compared with basal levels.

DISCUSSION

Combined oral contraceptives have been widely investigated and are well-known as an effective treatment for hirsutism (3). Although all achieve some reduction in serum androgen concentrations, their clinical benefit is blunted by variable androgenic activity of progestins within the formulations. The new DRSP containing COC Yasmin is considered a fourth generation COC due to the unique pharmacological activity of DRSP. This study demonstrated that an oral 30 μg EE/3 mg DRSP combination effectively suppressed hair growth in women with moderate to severe hirsutism, and that the positive affect varied among different body parts. The decline in hair growth was most prominent on the trunk and face. Major improvement occurred after 6 months of treatment and continued at a slower rate until the end of the study period. These results reflect the antiandrogenic properties of

TABLE 3

Hormone levels before and after oral EE/DRSP therapy.

Hormone	Basal	6 months	12 months	*P* value
FSH (mIU/mL)	5.9 ± 2.4	5.8 ± 2.0	5.4 ± 2.1	>.05
LH (mIU/mL)	6.1 ± 3.2	5.8 ± 3.3	6.0 ± 3.2	>.05
E_2 (pg/mL)	67.3 ± 26.1	67.7 ± 30.3	68.2 ± 29.3	>.05
SHBG (nmol/L)	35.8 ± 15.9	45.4 ± 23.5	51.4 ± 30.3	<.0001
DHEAS (μg/mL)	2.6 ± 1.2	2.6 ± 1.1	2.5 ± 1.3	>.05
A (ng/mL)	2.6 ± 0.8	2.4 ± 0.8	2.3 ± 0.8	.007
Total T (ng/dL)	88.7 ± 30.5	74.5 ± 25.1	71.6 ± 28.0	<.0001
Free T (pg/mL)	2.2 ± 1.5	1.9 ± 1.4	1.7 ± 0.9	.002

Note: Values are mean ± SD. EE/DRSP = ethinyl estradiol/drospirenone; FSH = follicle-stimulating hormone; LH = luteinizing hormone; E_2 = estradiol; SHBG = sex hormone-binding globulin; DHEAS = dehydroepiandrosterone sulfate; A = androstenedione; T = testosterone.

Batukan. The effect of Yasmin® in hirsutism. Fertil Steril 2006.

DRSP, which is explained by various mechanisms including a direct dose-dependent block of peripheral androgen receptors located on the dermis (4, 12).

Before beginning any medical therapy for hirsutism, it should be emphasized that the aim of treatment is not complete removal of excessive hair, but instead to achieve a slower growth rate necessitating less need for cosmetic intervention. Patients must be aware that only hair responsive to sex hormones, located on the face, chest, abdomen, and upper thighs, is amenable to medical therapy, and that medical therapy can only stop the conversion of vellus to terminal hair. Hair already transformed into terminal form is no longer receptive to medical therapy (1). Consistent with this data, a major improvement in decreased hair growth was observed on the chest and upper abdomen of our patients, whereas the arms and back were the most unresponsive regions. However, a decrease in facial hair growth of up to 90% was evident at the end of 1 year. The overall hirsutism score declined by 67% to 78% after 6 to 12 months, respectively. Others have reported similar, but somewhat lower, improvement of hirsutism in PCOS patients who were treated with the EE/DRSP combination (5, 7, 8). Guido et al. (7) stated that a clinically meaningful change of the F-G score occurred in 10 out of 15 hirsute patients with PCOS after treatment with 30 μg EE/3 mg DRSP for 12 cycles. Another study found that DRSP and cyproterone acetate containing COCs have similar efficacy on seborrhea and acne lesions as well as facial hair growth (5). Alternatively, Ibanez et al. (8) compared a low-dose flutamide plus metformin combination with EE/DRSP in 32 hirsute patients with PCOS. They reported that both regimens were comparable in terms of reducing hirsutism score, with an approximately 30% decrease in both groups during the course of 9 months of therapy.

Similar to other COCs, the combination of EE and DRSP is capable of reducing ovarian androgen synthesis, both by direct inhibition of enzymatic pathways involved in their biosynthesis and indirectly through suppression of gonadotropin secretion (4). The decline in serum T and A concentrations in our patients after 6 months are in concordance with these data. Others have reported similar changes (7, 8). The effect of EE/DRSP combination on adrenal steroid synthesis is less clear. Although it has been claimed that COCs may decrease adrenal androgen synthesis by a yet unknown mechanism, we did not observe any change in serum DHEAS concentrations during therapy with EE/DRSP. This is in contrast to the results of Guido et al. (7), who observed a significant decrease in serum DHEAS and 17-hydroxyprogesterone levels after 6 months.

Because COCs inhibit the hypothalamus-pituitary-ovarian axis, a significant decline in serum gonadotropin of these hormones would be expected, and most trials actually reported this finding (13–15). However, some studies did not find a significant change in serum gonadotropin levels, especially FSH, after treatment with COCs, and the decline in LH was evident in patients with an elevated basal level (16, 17). A significant change in serum LH, FSH, and E_2 concentrations during therapy with EE/DRSP combination was not observed in the present study. This is in accordance with the results of Guido et al. (7), who evaluated the efficacy of EE/DRSP in hirsute women with PCOS. They reported that serum FSH and E_2 concentrations did not change significantly after therapy with EE/DRSP combination throughout 12 cycles when compared with the baseline. However, their patients had elevated pretreatment LH levels, which markedly decreased after 3 months of treatment and remained stable thereafter.

The antiandrogenic activity of DRSP is further augmented by its lack of SHBG lowering effect. The resultant elevated SHBG levels are associated with decreased amount of biologically active free T. The increase in SHBG is reversible and steady-state concentrations were reached within 4–6 weeks after cessation of therapy with DRSP (18). Progestins derived from 19-nortestosterone (e.g., levonorgestrel, desogestrel, gestodene etc.) oppose or counteract the estrogen-induced increase in SHBG, resulting in a higher level of circulating free androgens, which means that they have an androgenic effect. We also observed a small but significant rise in SHBG during therapy with DRSP. However, results from other studies indicated a three to four times increase of SHBG over baseline levels after 9 to 12 months, which is greater than those reported in our study and after treatment with the most powerful antiandrogenic progestin cyproterone acetate (7, 8). The increase in SHBG would appear to be a major contributing factor in the antiandrogenic activity of EE/DRSP combination.

Despite their widespread use as a first line drug in the medical treatment of patients with hirsutism, oral COCs carry the potential risk of inducing venous thromboembolism and increasing arterial blood pressure. Obesity, which is frequently observed in patients with PCOS, increases the risk for thrombosis in itself, and hypertension commonly accompanies this syndrome. Therefore, care should be taken and one should be cautious when treating these patients with COCs. Recently, concern has been raised about the thrombotic risk of COCs containing 3 mg of DRSP and 30 μg of EE (19). van Vliet et al. (20) compared the prothrombotic changes in users of COCs containing either cyproterone acetate (CPA) or DRSP. They found that women using DRSP or CPA-containing COCs were more resistant to the anticoagulant action of activated prothrombin C than those using levonorgestrel-containing COCs. The authors advised not to prescribe DRSP-containing COCs as a first choice for women starting COC. Although these results pose some scientific evidence, it is obvious that results of randomized clinical trails are required to make recommendations that are more appropriate. Nevertheless, we did not observe any serious side effects during therapy with oral EE/DRSP combination, although some women complained of intermenstrual bleeding, headache, and breast tenderness. Because DRSP counteracts the mineralocorticoid activity of EE by

blocking aldosterone receptors at the distal renal tubules, estrogenic side effects due to sodium and fluid retention are blunted. This may increase patient compliance and has some protective effect against hypertension. However, it should be kept in mind that a COC containing 30 μg of EE and 3 mg of DRSP has the same contraindications as other COC formulations (12).

We conclude that the EE/DRSP combination exerts significant antiandrogenic activity and is especially effective in improving facial hirsutism. The beneficial effect is most obvious after six cycles and continues thereafter at a slower rate. The other advantages are minor side effects, which increase compliance to therapy.

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