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A prospective randomized trial comparing low-dose ethinyl estradiol and drospirenone 24/4 combined oral contraceptive vs. ethinyl estradiol and drospirenone 21/7 combined oral contraceptive in the treatment of hirsutism☆

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Abstract

Background: A prospective randomized trial was conducted to compare the clinical efficacy of two oral contraceptives containing drospirenone in the treatment of hirsutism in women.

Study Design: Fifty women with moderate to severe hirsutism were recruited. Three women were lost to follow-up. Twenty-four patients received oral 0.03 mg ethinyl estradiol and 3 mg drospirenone 21/7 regimen (Group 1) for 6 months. Another group of 23 patients received oral 0.02 mg ethinyl estradiol and 3 mg drospirenone 24/4 regimen (Group 2) for 6 months. Hirsutism was assessed after 6 months using the Ferriman–Gallwey (F-G) scoring system. Hormonal levels after 6 months of both therapies were compared with baseline values and each other.

Results: An improvement in the F-G scores for hirsutism (mean±SD) was observed in Group 1 (17.3±5.2 to 8.7±2.5, $p<.001$) and in Group 2 (17.5±4.8 to 7.9±2.8, $p<.001$). Pre- and post-treatment hirsutism scores were comparable between the groups ($p>.05$). Total and free testosterone levels decreased significantly after the therapy in both groups. The sex hormone-binding globulin levels increased significantly in both groups during the 6-month period.

Conclusion: The treatment of hirsutism with both combined oral contraceptives (COCs) containing drospirenone offered comparable effects and was well tolerated.

Keywords: Drospirenone; Ethinyl estradiol; Hirsutism; Combined oral contraceptive

1. Introduction

Hirsutism is defined as excessive growth of androgen-dependent sexual hair [1]. It affects 5–8% of the entire female population of reproductive age [2]. Not only is excessive hair growth a cosmetic problem, but it can also lead to psychological difficulties. Hirsutism may depend on excessive production of androgens or increased conversion of weak androgens to potent androgens [3].

The first-line treatment for women with hirsutism is the combined oral contraceptive (COC) pill [4]. Inhibition of luteinizing hormone (LH) secretion is mainly accomplished by addition of the progestational component and thus lowers the LH-mediated ovarian steroidogenesis, leading to decreased testosterone (T) production by the ovary. The estrogenic component decreases the androgenic effects of plasma T by increasing hepatic sex hormone-binding globulin (SHBG) synthesis [5]. However, this increase has not been shown to have a direct effect on hirsutism. The use of low-dose pills allows for suppression of T production while minimizing estrogen-related side effects [6].

The novel progestin drospirenone is a spironolactone analogue that has mineralocorticoid and antiandrogenic property. Its pharmacological profile more closely resembles that of natural progesterone compared to other progestins [7]. Additionally, this progesterone is incorporated in different hormone formulations, including the COC Yasmin® (Schering AG, Berlin, Germany) which contains drospirenone

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3 mg/ethinyl estradiol 0.03 mg, administered in cycles of 21 days continuous use followed by a 7-day hormone-free interval (21/7). This agent has reliable contraceptive effects with safety profile and beneficial properties for acne and seborrhea [8,9]. In the treatment of hirsutism, Batukan and Muderris [10] showed that this COC was effective in patients with or without polycystic ovary syndrome (PCOS). In a recent study, this COC has been shown to have favorable effects on hirsutism with better outcomes on lipid, glycemic and hormonal profile in women with PCOS than desogestrel-containing COC [11].

A new low-dose COC, Yaz® (Bayer Schering Pharma, Weimar, Germany), containing drospirenone 3 mg/ethinyl estradiol 0.02 mg has been developed that comprises a regimen with 24 active pills and four inert pills (24/4). This COC is efficient for birth control with an acceptable bleeding pattern and useful for the treatment of premenstrual dysphoric disorder and acne vulgaris [12–14]. The purpose of the present study was to report our clinical and biochemical results with two COCs containing drospirenone and different dosages of ethinyl estradiol in hirsute patients with or without PCOS. To our knowledge, no study comparing these two COCs has been performed in patients with hirsutism.

2. Materials and methods

This prospective randomized clinical trial was conducted on a population of unselected 50 women with moderate and severe hirsutism after obtaining ethical approval from the University Ethics Committee. 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) <7000 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 typically appearing ovaries (i.e., eight or more peripherally arranged discrete follicles with or without an enlarged hyperechogenic central stroma) were diagnosed with PCOS [15].

A detailed history, including menstrual history and past medical history, was taken. Each patient underwent a complete medical examination, in addition to a hormonal profile, and hepatic and renal function analyses. Those who had been taking any medication, including a COC or long-acting progestins during the last 12 months before the enrollment, were excluded. To avoid interobserver errors, the same physician (I.I.M.) who was blinded to the treatments graded the degree of hirsutism according to a modified Ferriman-Gallwey (F-G) scoring system [16]. Patients were asked not to epilate during the treatment. Nine body areas were evaluated for density and area of hair growth and quantified on a 0- (*no hirsutism*) to 4-point (*severe*) scale. The patients with a score of 8 or more were included in the study. The body mass index (BMI) was calculated according to the following formula: body weight in kilograms/height in meters squared, and the patients were instructed not to modify their usual diet during the study.

After obtaining informed consent, participants were randomized using a computer-generated randomization table into two groups, as depicted in Fig. 1. Group 1 (n=25) received a daily oral 0.03 mg of ethinyl estradiol plus 3 mg of drospirenone combination (Yasmin®) as a 21/7-day regimen and Group 2 (n=25) received a daily oral 0.02 mg of ethinyl estradiol plus 3 mg of drospirenone combination (Yaz®) as a 24/4-day regimen for 6 months.

Patients were followed up for 6 months during the treatment. Serum samples for hormone analysis were taken before the therapy at early follicular phase in women with regular menstrual cycles or on a convenient day for those who were amenorrheic. At the end of the 6-month treatment, blood samples were collected between Day 3 and Day 6 after the withdrawal bleeding of the previous cycle. During the therapy, all hirsute women had an interview in order to establish the course of the menstrual cycle and side effects.

Serum follicle-stimulating hormone (FSH), LH, total T, free T, androstenedione (A), estradiol (E2) (DSL-4900, Diagnostic Systems Laboratories, Webster, TX, USA) and DHEAS (Immunotech, Marseilles, France) were measured by radioimmunoassay; SHBG was measured by immunoradiometric assay (Orion Diagnostica, Espoo, Finland), using commercial kits in the biochemical laboratory of the University of Erciyes. The intra-assay 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 E2, 5.6% and 4.1% for DHEAS, and 4.0% and 5.5% for SHBG, respectively.

Numerical variables were presented as means±SD. Non-normally distributed metric variables were analyzed by Kruskal–Wallis test and Mann–Whitney U test. After the confirmation of normal distribution, paired and unpaired t tests were used to compare the values before and after the treatment in the women studied. $p \leq .05$ was considered

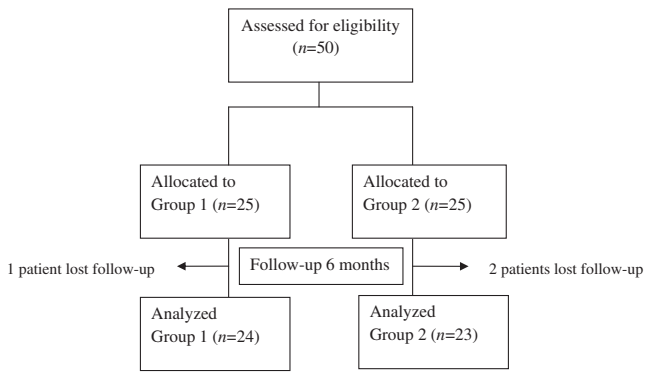

Fig. 1. CONSORT Flow diagram showing the progress of the study.

statistically significant. All analyses were performed using the Statistical Package for the Social Sciences, version 15.0 (SPSS, Chicago, IL, USA).

3. Results

Forty-seven women completed the study; three women were lost to follow-up, and their results are not presented. All patients tolerated the COCs well without serious complaints or side effects necessitating the discontinuation of the therapy. BMI (mean±SD) (23.4±4.6 vs 23.9±6.6) and age (23.5±4.4 vs. 22.5±4.6) of the patients were similar between Group 1 and Group 2. At the end of the treatments, no significant variations were seen for BMI within the same group and between the groups (23.2±4.2 vs. 23.4±4.6). Ten patients were obese (BMI $\geq$30 kg/m^2).

Prior to the treatment, 12 (50%) of 24 and 12 (52%) of 23 had oligo/amenorrhea in Group 1 and Group 2, respectively. During the treatment, cycles became regular in all patients in both groups. Five patients had intermenstrual bleeding in Group 1 and four patients in Group 2 during the treatments.

Table 1 shows the hormone levels and hirsutism scores before and after 6 months of therapy in Groups 1 and 2. An improvement in the mean F-G scores for hirsutism was observed in Group 1 (17.3±5.2 to 8.7±2.5, p<.001) and in Group 2 (17.5±4.8 to 7.9±2.8, p<.001). The hirsutism scores before the treatment and at the end of 6 months were comparable between the groups (p>.05).

There were no significant differences in mean levels of FSH, LH, E2, A and DHEAS in both groups (p>.05). Additionally, there were no changes in these hormones after the treatments in both groups (p>.05). Total and free mean T levels decreased significantly after the therapy in both groups (p<.05), whereas there were no statistically significant differences between the groups. The mean SHBG levels were increased significantly by the end of the 6-month period in both groups when compared with basal levels; no significant differences were found between the groups (p>.05) (Table 1).

4. Discussion

The drugs most commonly used to treat hirsutism include oral contraceptives, gonadotropin-releasing hormone analogs, androgen receptor antagonists and corticosteroids. COCs have been extensively used to treat hirsutism [3]. This report summarizes the findings of a randomized prospective trial comparing the effects of both a 21/7 regimen and a 24/4 regimen in women with hirsutism. Beneficial effects of a COC containing drospirenone on hirsutism have been previously reported [3,10]. However, this is the first randomized study directly comparing two drugs containing drospirenone. Additionally, no study has been found on the treatment of hirsutism with low-dose ethinyl estradiol and drospirenone 24/4 COC in the literature.

The antiandrogenic activity of drospirenone is augmented by the elevating effect of ethinyl estradiol on SHBG. Therefore, the increase in SHBG levels is associated with decreased levels of active free T [17]. We also observed a significant rise in SHBG levels during both therapies with drospirenone and ethinyl estradiol. So, the increase in SHBG would appear to be a major factor in the antiandrogenic activity of both treatment regimens. Although estrogen increases the circulating levels of SHBG, the SHBG levels were similar with the 0.02-mg ethinyl estradiol–drospirenone and the 0.03-mg ethinyl estradiol–drospirenone COC.

In the present study, no significant changes in serum FSH, LH and E2 levels during both therapies were observed. A previous study reported similar findings [10]. However, in another study, LH levels markedly decreased after the treatment [18]. The effect of ethinyl estradiol and drospirenone combination on adrenal steroid synthesis is unclear. Although it has been claimed that COCs may decrease adrenal androgen synthesis by a yet-unknown mechanism,

Table 1
Effects of treatment on hormonal profile and hirsutism score in both groups

	Basal		6 months	
	Group 1 (*n*=24)	Group 2 (*n*=23)	Group 1 (*n*=24)	Group 2 (*n*=23)
FSH (mIU/mL)	5.8±1.2[a]	5.8±1.7[a]	5.8±1.7[a]	6.1±1.8[a]
LH (mIU/mL)	6.9±0.4[a]	6.8±0.4[a]	7.0±0.3[a]	6.9±0.3[a]
Estradiol (pg/mL)	67.6±11.0[a]	68.4±11.4[a]	68.1±9.8[a]	68.1±10.4[a]
SHBG (nmol/L)	45.3±22.1[a]	48.1±30.2[a]	62.8±30.9[b]	70.1±58.6[b]
DHEAS (mcg/mL)	2.6±1.3[a]	2.6±1.3[a]	2.6±2.0[a]	2.6±1.4[a]
A (ng/mL)	2.9±0.3[a]	3.0±0.1[a]	2.8±0.2[a]	2.9±0.3[a]
Total T (ng/dL)	87.5±43.7[a]	80.5±40.5[a]	58.7±22.8[b]	61.0±36.4[b]
Free T (pg/mL)	2.9±0.9[a]	2.8±0.7[a]	2.1±0.5[b]	2.1±0.8[b]
Hirsutism score	17.3±5.2[a]	17.5±4.8[a]	8.7±2.5[b]	7.9±2.8[b]

Values are mean±SD. FSH=Follicle-stimulating hormone; LH=luteinizing hormone; SHBG=sex hormone-binding globulin; DHEAS=dehydroepiandrosterone sulfate; A=androstenedione; T=testosterone.
Statistically significant difference is not present in groups sharing the same letter (a or b, p>.05).
Statistically significant difference is present in groups sharing a different letter (a and b, p<.05).

we did not observe any change in serum DHEAS levels during both therapies.

In a recent study, the COC formulation of 0.02 mg of ethinyl estradiol plus 3 mg of drospirenone provided a well-tolerated bleeding profile with a low discontinuation rate [12]. Additionally, treatment-related adverse events were reported such as pelvic pain, headaches, bloating and breast tenderness for COCs, which were less commonly reported by women during the treatment period of 24/4 regimen [19]. An extended contraceptive regimen and a shortened hormone-free interval may reduce the incidence of hormone withdrawal symptoms. Furthermore, reducing the number of hormone-free days has been shown to result in more pronounced ovarian suppression, which is expected to increase contraceptive effectiveness. In our study, no patient discontinued the treatment with the low-dose ethinyl estradiol and drospirenone 24/4 COC.

Drospirenone is a novel progestogen with antimineralocorticoid, progestogenic and antiandrogenic activity. This combination is well tolerated, demonstrating good cycle control and a beneficial effect on skin condition and well-being [20]. Recently, in patients with PCOS, drospirenone-containing COCs had better outcomes in terms of clinical and hormonal profiles than other COCs [11]. The drospirenone-plus-ethinyl estradiol combination is at least as effective as the cyproterone acetate-plus-ethinyl estradiol combination in improving hirsutism scores [21]. The 24/4 COC containing drospirenone had some extra contraceptive benefits such as improving acne, hirsutism and premenstrual symptoms [22]. Also, one of the regimens containing drospirenone such as 24/4 was comparable with traditional 21/7 COC dosing regimen for safety and efficacy [23]. In the present study, two COCs had similar side effects and comparable efficacies.

In conclusion, oral 0.02 mg ethinyl estradiol plus 3 mg drospirenone 24/4 regimen and oral 0.03 mg ethinyl estradiol plus 3 mg drospirenone 21/7 regimen have comparable outcomes. In patients with hirsutism, both COCs containing drospirenone had favorable outcome measurements in terms of regularity of cycles, hormonal profiles and antiandrogenic effects after six cycles. The new 24/4 COC agent provides effective treatment on hirsutism. Consequently, the new COC formulation of 0.02 mg of ethinyl estradiol plus 3 mg of drospirenone may be well tolerated and safely used in the treatment of hirsutism.

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