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Psychological effect of the oral contraceptive formulation containing 3 mg of drospirenone plus 30 μg of ethinyl estradiol

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Objective: To investigate in healthy eumenorrheic young women whether an oral contraceptive (OC) containing drospirenone (DRSP) (3 mg) + ethinyl estradiol (EE) (30 μg) (DRSP + EE) could modify psychological symptoms and whether it could modify steroids interfering with the γ-aminobutyric acid (GABA)-A receptors.

Design: Clinical study of treated subjects and nontreated controls.

Setting: Healthy volunteers in the Department of Obstetrics and Gynecology at Cagliari University.

Patient(s): Control group (n = 12) and OC group (n = 10) women with similar age, body mass index, and main outcome measures.

Intervention(s): The control group was studied during the first menstrual cycle at the follicular phase (FP) and at the luteal phase (LP) and during the third cycle at the LP; the OC group was studied during the first cycle, as described above, and on day 16–18 of the third cycle of treatment with DRSP + EE.

Main Outcome Measure(s): Psychometric scale (SCL-90), DHEAS, P, allopregnanolone (AP), and allotetrahydrodeoxy-corticosterone (THDOC).

Result(s): SCL-90 and DHEAS did not vary throughout the menstrual cycle. P, AP, and THDOC values were higher during the LP than the FP. At the third cycle, in the control group the main outcome measures were similar to those at LP. In the OC group, the SCL-90 global score, the intensity of anxiety and phobic anxiety, the levels of anxiolytic steroids (P, AP, THDOC) and the anxiety-inducing steroid DHEAS were reduced.

Conclusion(s): The results suggest beneficial effects of DRSP + EE on psychological symptoms by decreasing DHEAS. (Fertil Steril® 2004;81:645–51. ©2004 by American Society for Reproductive Medicine.)

Key Words: Drospirenone, neuroactive steroids, DHEAS, SCL-90 psychometric scale, oral contraceptive formulations

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Changes in mood, specifically depression, is one of the most common reasons given for discontinuing oral contraceptive (OC) use (1). The γ-aminobutyric acid (GABA)-A receptors participate in the regulation of a variety of psychological phenomena, including anxiety, sleep, depression, seizures, and sexual dysfunction (2–4). Recent studies have shown that the P metabolites 3α hydroxy-5α-pregnan 20-one (allopregnanolone, AP) and 3 α,21-dihydroxy-5α-pregnan-20-one (allotetrahydrodeoxy-corticosterone, THDOC) rapidly affect the excitability of neurons through direct modulation of the activity of GABA-A receptors (5, 6). AP and THDOC are steroids with neuroactive properties. They can be synthesized in the adrenal glands, gonads, feto-placental unit, and several brain regions that are equipped with enzymes necessary for steroid hormone biosynthesis (7), either directly from cholesterol or from the P precursor (8). In contrast to AP and THDOC, DHEAS and pregnenolone sulfate display functional antagonist properties as allosteric modulators of the GABA-A receptors (9, 10).

A recent paper by Follesa et al. (11) shows that in women taking OCs there is a significant decrease in circulating levels of P, AP, and

THDOC. Decreased values of neuroactive steroids are an expected occurrence with OCs as a consequence of suppressed endogenous P values (12). However, the study by Follesa et al. (11) seems to suggest that the synthetic steroids of OCs may directly regulate the activity or expression of enzymes that catalyze the biosynthesis of neurosteroids, thereby selectively affecting the accumulation of these latter compounds in the brain. In particular, the progestin compound could be involved in this occurrence, as suggested by previous studies indicating that the progestogenic compound levonorgestrel is capable of inhibiting 5α reductase in the skin (13).

Drospirenone (DRSP) is a 17-α-spironolactone derivative with pharmacological properties that uniquely combine progestogenic, antimineralcorticoid, and antiandrogenic activity but without estrogenic and androgenic activity (14–16). It is being developed in combination with ethinyl estradiol (EE), and a preparation containing 3 mg DRSP and 30 μg EE has been shown to provide effective oral contraception (OC), excellent cycle control, and good tolerability. DRSP also exerts antimineralcorticoid effects that may have a key role in improving the compliance in women with a tendency to weight gain due to water retention (17).

A recent study shows that the OC containing 3 mg DRSP + 30 μg EE induces a trend in the reduction of somatic symptoms in women with premenstrual dysphoric disorders (18). The aim of this study was to evaluate some neuroactive steroids and psychological symptoms in healthy women taking OCs containing 3 mg DRSP + 30 μg EE compared with a matched group of nontreated controls.

SUBJECTS AND METHODS

Assessment of Psychological Symptoms

To assess psychological symptoms and their intensity, an Italian psychometric self-report clinical scale validated in healthy women was used (SCL-90) (19). SCL-90 is oriented toward the psychiatric outpatient's symptomatology. It includes 90 items that focus on the assessment of anxiety, depression, interpersonal sensitivity, obsessive-compulsive symptoms, hostility, psychoticism, somatization, phobic anxiety, and paranoid ideation (19).

Subjects

The subjects included in the study were 30 healthy women (mean age, 25 ± 1 years) with a body mass index [BMI, weight (Kg)/height (m^2)] greater than 21, but less than 23, with regular menstrual cycles and without past or present psychological or mood disorders, thyroid diseases, or family history for the above illnesses. Regular menstrual cycle was defined as a menstrual flow occurrence every 28–30 days, with a duration of about 4–6 days and without the occurrence of spotting or breakthrough bleeding episodes. The subjects were recruited from the women who referred to the Department of Obstetrics and Gynecology of the University of Cagliari asking for contraception. Twenty (mean age, 25.25 ± 0.67 years) of these subjects asked for contraception with natural methods and gave their informed consent to participate in the study as volunteers (control group). The remaining 10 subjects of a similar age (mean age, 23.6 ± 0.74 years) asked for OC and participated in the study as volunteers (OC group).

Before inclusion in the study, all subjects gave their informed consent. Likewise, before inclusion in the study, subjects prone to contraindications to OC intake were excluded, in accordance with World Health Organization guidelines (20).

Method

Control Group

All women were invited to have three visits at the Department of Obstetrics and Gynecology. The first two visits occurred during the first menstrual cycle of the study: the first visit occurred on a day between day 3 and day 8 from the onset of menstrual bleeding (follicular phase, FP), and the second visit occurred on day 5–8 from the increase of body basal temperature (luteal phase, LP) (second visit). The third visit occurred at the LP, as previously described, during the third menstrual cycle of the study.

OC Group

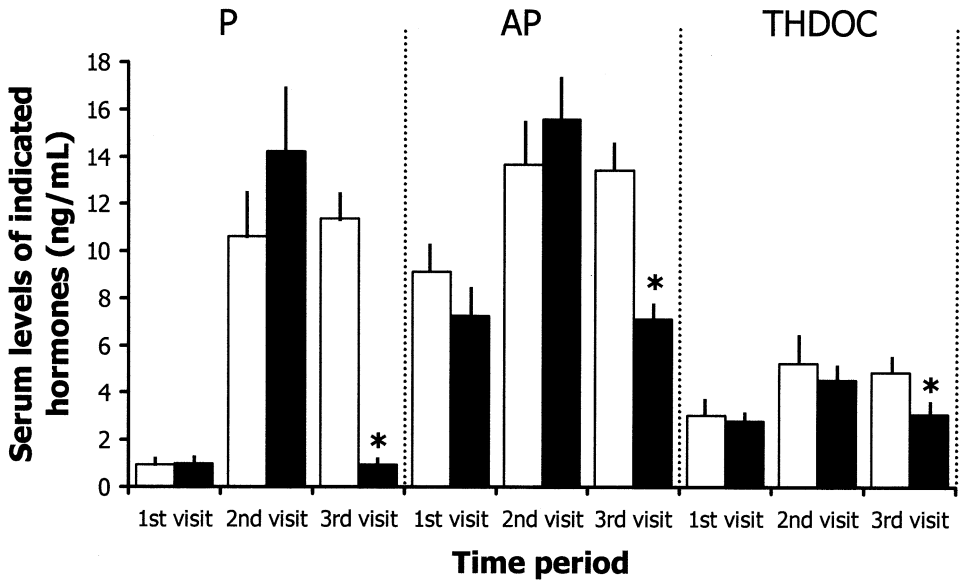
In the OC group, the visits occurred at the following times: during the menstrual cycle before commencing OC intake when the women were on a day of the FP (first visit) and on a day of the LP (second visit), as described for control women; and during the third cycle of the intake of the OC containing 3 mg DRSP + 30 μg EE, when the women had taken the 16th–18th OC combined formulation (third visit).

Each visit was performed in the morning between 8:00 and 10:00 A.M. After an overnight fast, the women were submitted to venipuncture of an anterocubital vein to collect blood samples. Before or after the blood collection, according to the preference expressed by the women, each subject was invited to fill in a SCL-90 scale. During each visit, all subjects included in the study were asked about the frequency, intensity, and duration of menstrual flows and the occurrence of spotting or breakthrough bleeding episodes. Blood pressure, weight, height, and waist-to-hip ratio (WHR) were measured at each visit.

All blood samples were collected in tubes containing clot-activating factor and were immediately centrifuged. The serum samples were stored at −80°C until assayed. At the end of the study, the following parameters were evaluated in each serum sample: LH, FSH, E_2, P, total T (tT), cortisol, androstenedione (A), sex hormone–binding globulin (SHBG), DHEAS, AP, and THDOC. The serum samples of each subject were measured in the same assay to avoid the interferences between assays.

FIGURE 1

Mean ± SE of circulating serum levels of P (**left-hand graph**), AP (**middle graph**), and THDOC (**right-hand graph**) measured during the 3-month period of the study in the control group women (*open bars*) and in the study group women (*dark bars*). In the study group women, the values of P, AP, and THDOC are significantly lower (*$P<.04$) than those measured in the same subjects at the second visit and significantly lower (*$P<.04$) than those measured in the control group women both at the second and at the third visit.



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The assay of P, AP, and THDOC was performed at the Department of Experimental Biology, and the other parameters were measured at the Department of Obstetrics and Gynecology. The assay of P, AP, and THDOC was performed by radioimmunoassay as described elsewhere (21). The concentrations of P, AP, and THDOC were measured in 1 mL of serum after extraction four times with 1.5 mL of ethyl acetate. P, AP, and THDOC were obtained from Sigma (Milan, Italy). Rabbit or sheep antiserum to AP or to THDOC was generated and characterized as described elsewhere (22). Antiserum to P was obtained from ICN (Costa Mesa, CA). All other reagents and organic solvents (high pressure liquid chromatography grade) were of the best quality available from commercial sources.

LH, FSH, E_2, tT, SHBG, cortisol, DHEAS, and A were assayed by commercial kits (Adaltis, Casalecchio di Reno, Italy, for E_2 and A; Medical System, Genova, Italy, for tT, SHBG, cortisol, and DHEAS; Biomerieux, Marcy l'Etoile, France, for LH and FSH). For each assay, the sensitivity was very good. The coefficients of variation of these assays were not greater than 7.7% (intra-assay) and 8.1% (interassay). At the end of the study, all SCL-90 scales were examined blindly by one of the authors (SF).

Statistical analysis of the results was performed using the Student's *t*-test for paired or unpaired data. One- or two-factor analyses of variance for repeated measures were also used. All results are expressed as mean ± SE.

The study was approved by the local ethics committee and the Institutional Review Board.

RESULTS

Only 12 of the 20 subjects among the women in the control group completed the study. Personal reasons prevented the remaining eight subjects from completing the study. In the OC group, no subject interrupted the study. Therefore, the data reported in the results are calculated from a total of 12 women in the control group (mean age, 24.2 ± 0.72 years) and 10 women in the OC group (mean age, 23.6 ± 0.74 years). The OC group did not differ from the control group in each parameter examined both at the FP and at the LP of the menstrual cycle. In the control group, the values of each parameter examined at the third visit did not differ from those at the second visit. In addition, no changes of the menstrual cycle characteristics occurred in these subjects.

Similarly, in the OC group the BMI and WHR at the third month of the study did not differ from those measured in the same subjects during the FP and LP of the menstrual cycle preceding the treatment (Table 1). There was no difference in blood pressure during the treatment than before the treat-

TABLE 1

Mean ± SE of hormonal, psychometric and clinical parameters in the study group (n = 10) during the follicular and luteal phase of the menstrual cycle before treatment and at the third cycle of treatment with oral contraceptive containing 3 mg of DRP + 30 μg of ethinyl E_2

	Follicular phase (first visit)	Luteal phase (second visit)	Luteal phase of third cycle (third visit)	Statistical value (third visit versus first and second visit)
Body mass index	20.91 ± 0.56	21.12 ± 0.67	21.17 ± 0.88	Not significant vs. first and second visit
Waist-to-hip ratio	0.78 ± 0.02	0.77 ± 0.02	0.77 ± 0.02	Not significant vs. first and second visit
LH (mIU/mL)	5.87 ± 1.00	3.27 ± 0.50	1.73 ± 0.71	$P < .005$ vs. first and second visit
FSH (mIU/mL)	4.92 ± 0.82	3.56 ± 0.49	2.14 ± 1.11	$P < .005$ vs. first and second visit
E_2 (pg/mL)	42.60 ± 12.00	74.10 ± 13.80[a]	17.20 ± 4.50	$P < .05$ vs. first and second visit
P (ng/mL)	0.98 ± 0.36	14.23 ± 2.78[a]	0.94 ± 0.25	$P < .0001$ second visit
Total T (pg/mL)	414.0 ± 60.0	474.0 ± 78.0	280.0 ± 34.0	$P < .05$ vs. first and second visit
Sex hormone–binding globulin (SHBG) (nM/L)	57.02 ± 4.37	61.83 ± 6.50	156.3 ± 12.12	$P < .0001$ vs. first and second visit
Free androgen index (total T/ SHBG)	7.50 ± 1.03	9.13 ± 2.20	1.95 ± 0.25	$P < .02$ vs. first and second visit
A (ng/mL)	2.14 ± 0.18	2.06 ± 0.21	1.73 ± 0.14	$P < .005$ vs. first and second visit
Cortisol (ng/mL)	172.9 ± 21.4	146.1 ± 18.0	370.8 ± 54.6	$P < .003$ vs. first and second visit
DHEAS (μg/mL)	1.36 ± 0.22	1.46 ± 0.15	0.99 ± 0.13	$P < .03$ vs. first and second visit
Allopregnanolone (ng/mL)	7.25 ± 0.30	15.57 ± 2.48[a]	7.10 ± 0.52	$P < .004$ vs. second visit
Allotetrahydrodeoxy-corticosterone (ng/mL)	2.82 ± 0.35	4.55 ± 0.47[a]	3.08 ± 0.33	$P < .007$ vs. second visit
SCL-90 (global score)	43.6 ± 9.40	44.9 ± 9.90	30.00 ± 6.50	$P < .05$ vs. first and second visit
Intensity of				
Depression	0.683 ± 0.148	0.689 ± 0.144	0.427 ± 0.112	Not significant vs. first and second visit
Anxiety	0.488 ± 0.100	0.500 ± 0.105	0.300 ± 0.085	$P < .02$ vs. first and second visit
Phobic anxiety	0.123 ± 0.047	0.126 ± 0.049	0.042 ± 0.030	$P < .05$ vs. first and second visit
Hostility	0.522 ± 0.138	0.531 ± 0.140	0.281 ± 0.108	Not significant vs. first and second visit
Paranoid ideation	0.518 ± 0.123	0.547 ± 0.124	0.312 ± 0.112	$P < .05$ vs. first and second visit
Psychoticism	0.240 ± 0.083	0.230 ± 0.084	0.190 ± 0.080	Not significant vs. first and second visit
Interpersonal sensitivity	0.293 ± 0.125	0.287 ± 0.121	0.188 ± 0.099	Not significant vs. first and second visit
Somatization	0.463 ± 0.127	0.522 ± 0.130	0.413 ± 0.083	Not significant vs. first and second visit
Obsessive compulsive disorder (OCD)	0.537 ± 0.129	0.530 ± 0.121	0.340 ± 0.110	Not significant vs. first and second visit

[a] $P<.04$ vs. first visit.

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ment. During the 3 months of treatment, spotting or breakthrough bleeding did not occur in the women of the OC group, and the menstrual cyclicity was 25 ± 3 days during the first cycle and 28 ± 2 days during the second month of treatment. At the third month of treatment (third visit), in the OC group subjects LH, FSH, E_2, tT, and A values were significantly lower than those measured in the same subjects during the FP and the LP of the cycle preceding the treatment (Table 1). On the contrary, SHBG and cortisol levels were significantly higher during the third month of treatment than before treatment (Table 1). Consequently, the free androgen index, which represents the tT to SHBG ratio, was significantly lower during the treatment than before (Table 1).

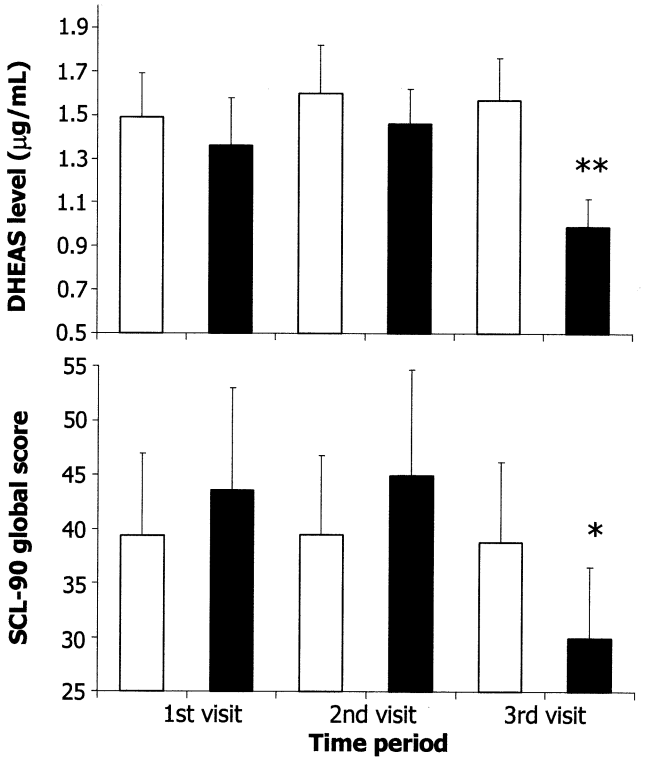
At the third month of treatment (third visit), the values of P, like those of AP and THDOC, were significantly lower in the OC group than those measured in the same subjects during the LP of the cycle before the treatment (second visit) and those measured in the control group both at the second and at the third visit (Fig. 1). However, they did not differ from those measured during the FP before the treatment (first visit) (Fig. 1) and the FP values of the control group women (first visit) (Fig. 1).

At the third month of the study, the values of DHEAS were significantly lower in the OC group than those measured at the FP and the LP (Fig. 2) and those of the control group subjects at every time period of the study (Fig. 2). At the third month of the study, the total score of SCL-90 was significantly lower in the OC group than that measured in the same subjects during the FP and LP of the menstrual cycle (Fig. 2) and than that measured in the control group subjects at every time period of the study (Fig. 2).

As for each symptom evaluated by the SCL-90 scale, the intensity of anxiety, phobic anxiety, and paranoid ideation was significantly lower in the OC group during the third

FIGURE 2

Mean ± SE of circulating serum levels of DHEAS (**top graph**) and mean ± SE of the SCL-90 global score (**bottom graph**) measured during the 3-month period of the study in the control group women (*open bars*) and in the study group women (*dark bars*). At the third visit, in the study group subjects the values of DHEAS and the SCL-90 global score are significantly lower (**$P<.03$; *$P<.05$) than those measured both in the same subjects and in the control subjects at the first and second visit.



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month of treatment (third visit) than during the FP and the LP of the menstrual cycle before treatment and than that calculated in the control group at each time period of the study (Fig. 3). The intensity of the other items (depression, obsessive compulsive disorder, interpersonal sensibility, hostility, somatization, and psychoticism) was lower than before treatment, but the decrement was not significant for the statistical analysis (Fig. 3).

DISCUSSION

The findings of this study can be applied to a population of healthy women without psychological diseases and without psychological premenstrual symptoms. In fact, the healthy women participating in the study did not suffer from premenstrual symptoms, as shown by the evaluation of psychometric SCL-90 scale, the values of which did not vary between FP and LP of the menstrual cycle. Likewise, DHEAS values did not vary throughout the menstrual cycle. Although it is known that DHEAS exerts a potent anxiety-inducing effect by acting as an antagonist of the GABA-A receptors (9, 10), contrasting data about the role exerted by DHEAS on psychological symptoms are reported in humans. High DHEAS levels were shown in association with high anxiety scores (23), as well as with post-traumatic stress disorder (24) and unipolar major depression (25). However, other studies showed that DHEAS levels are significantly and inversely associated with depressed mood (26, 27).

This study seems to suggest that DHEAS could play an important role in the control of psychological symptoms. In fact, in healthy women stable values of the anxiety-inducing factor DHEAS are associated with stable psychological symptoms throughout the menstrual cycle, and this pattern occurs in spite of increased luteal values of the anxiolytic factors P, AP, and THDOC. The subjects of the control group did not differ from those of the OC group. However, at the third month of the study, there was a significant improvement of psychological symptoms in the OC group, whereas no changes occurred in the control women. Since at the third month of the study the only variable factor between the OC group and the control group was the intake of the 30 μg EE + 3 mg DRSP OC formulation, it is likely that the improvement of psychometric parameters in the OC group women could be dependent on the treatment.

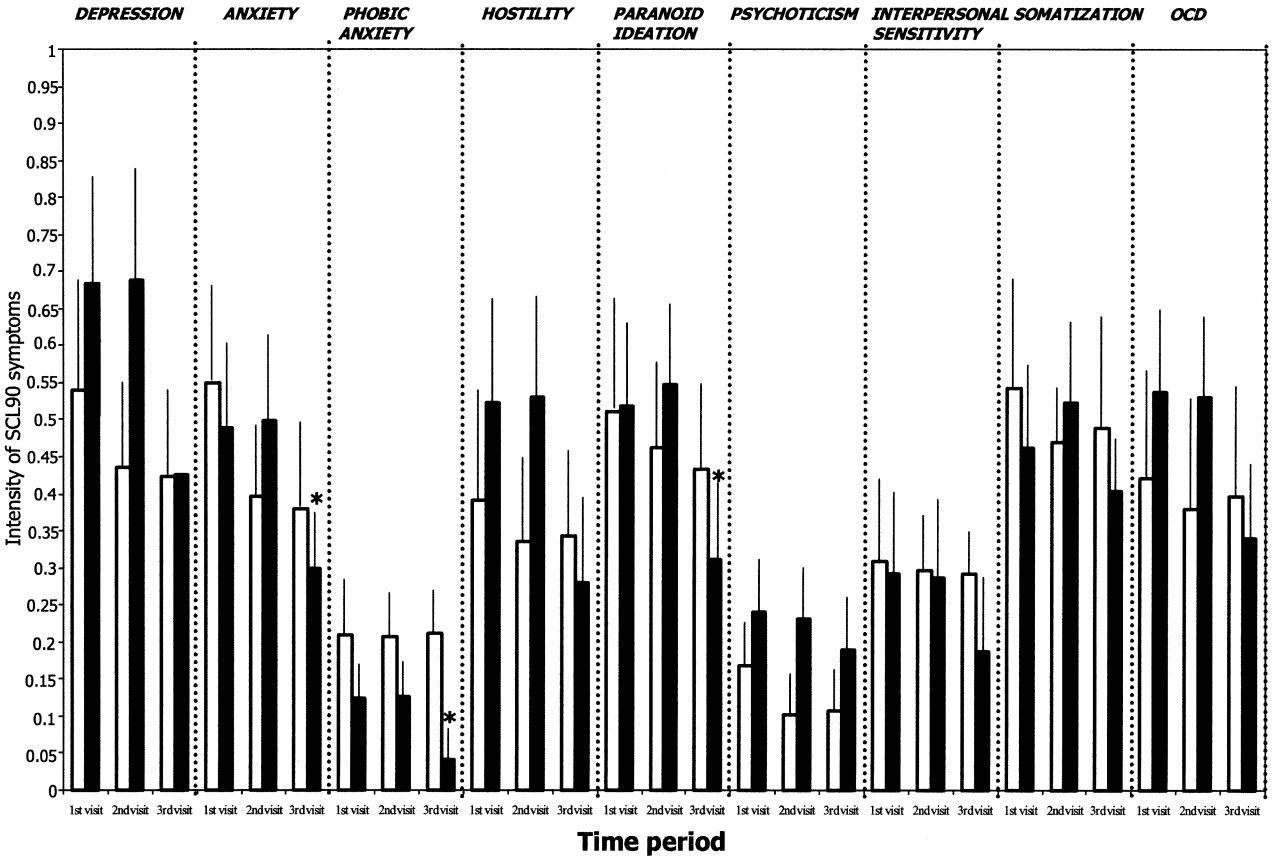
Despite the limited number of subjects and the fact that the study was not randomized, blinded, or placebo controlled, this observation "per se" is very important. In fact, it seems to suggest that the 30 μg EE + 3 mg DRSP OC formulation could have beneficial effects on psychological symptoms that are not reported with other OC formulations (1).

The study also seems to suggest a possible mechanism through which the 30 μg EE + 3 mg DRSP OC formulation could improve psychological symptoms. Similar to that described with other OC formulations (11), in the OC group at the third month of 30 μg EE + 3mg DRSP treatment there was a significant decrease in P, AP, and THDOC. A significant decrease of DHEAS levels, which was never described in women treated with other OCs and which did not change in nontreated women, was also observed. More than the decrease of the SCL-90 global score, it is important to point out that decreased DHEAS values were associated with a decreased intensity of some items (anxiety, phobic anxiety, and paranoid ideation), which can come from the anxiety-inducing effect of DHEAS (9, 10, 23). Moreover, the decrease of P, AP, and THDOC cannot justify the improvement of psychological symptoms since these steroids are well-known anxiolytic agents acting on GABA-A receptors.

The study did not investigate the mechanism by which the 30 μg EE + 3 mg DRSP OC formulation reduces DHEAS circulating levels, nor if the same changes could also occur

FIGURE 3

Mean ± SE of the values of each symptom evaluated by the SCL-90 psychometric scale, as indicated in the figure, during the 3-month period of the study in the control group women (*open bars*) and in the study group women (*dark bars*). At the third visit, in the study group women the intensity of anxiety, phobic anxiety, and paranoid ideation is significantly lower (*$P<.05$) than that measured in the same subjects at the first and second visit and than that measured in the control group women at every time period in the study.



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with OC formulations containing different progestin compounds. With regard to the latter, it would be interesting to investigate whether DRSP could modulate some central neurotransmitters, as suggested with other progestin compounds included in menopausal replacement formulations (28, 29). Further studies are needed to evaluate whether DRSP acts through a central mechanism or through peripheral mechanisms deriving from its pharmacological properties (14–16). Finally, it cannot be ignored that, independent of the DRSP properties, these findings could also derive from a mechanism exerted by the association of DRSP with 30 μg EE rather than with different EE dosages.

Despite the study design limitations and the fact that biases and placebo effect could account for differences in symptoms between the control and OC subjects, in young eumenorrheic healthy women the OC containing 30 μg EE + 3 mg DRSP seems to improve the global score of the psychometric scale SCL-90 and to decrease DHEAS, a steroid with anxiety-inducing properties at the GABA-A receptors.

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