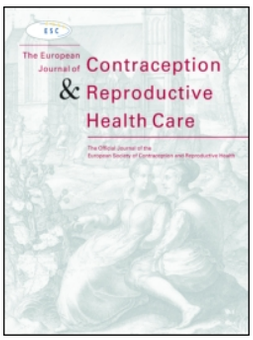

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CLINICAL STUDY

Mood disturbances during combined oral contraceptive use and the effect of androgen supplementation. Results of a double-blind, placebo-controlled, single-case alternation design pilot study

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ABSTRACT

Objectives: To evaluate the effect of androgen supplementation in healthy combined oral contraceptive (COC) users who experience mood disturbances during COC-use only.

Methods: Six women with mood disturbances during COC-use only, received COC with co-treatment of 50 mg dehydroepiandrosterone (DHEA) during three cycles and placebo during another three cycles in an individualized random order. Daily mood rating was measured by a single item: 'In what kind of mood have you been in the past 24 h?' The results were analysed using a randomisation test for single-case experimental designs.

Results: The *p* values for the alternation design randomisation tests on the raw data of the six healthy individuals varied between 0.21 and 1, indicating that the average daily mood ratings of the active treatment DHEA are not statistically significantly larger than the average daily mood ratings of placebo. The combined *p* value of the subjects using a DRSP-containing pill was 0.97, and of the subjects using an LNG-containing pill was 0.65, indicating no statistically significant treatment effect for any of the pill types.

Conclusions: In this single-case alternation design study, concomitant treatment with DHEA for intermittent periods of 4 weeks did not result in improvement of mood disturbances related to COC-use, but had also no side-effects.

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Androgen; androgen supplementation; combined oral contraceptive; mood; mood disturbance; oral contraceptive pill

Introduction

Although reported effects of combined oral contraceptives (COCs) on well-being and mood in the literature are inconsistent and often contradictory [1,2], a subgroup of women do experience negative mood changes during COC-use [3]. A recent prospective cohort study reported that use of hormonal contraception, especially among adolescents, was associated with subsequent use of antidepressants and a first diagnosis of depression, suggesting depression as a potential adverse effect of hormonal contraceptive use [4]. The potential negative effects of COC on mood may cause discontinuation and switching [5]. Young women with adverse psychological symptoms are at risk for perceived COC side effects and discontinuation [6,7].

COCs decrease circulating levels of total testosterone (T) and free T. This decrease is caused by an inhibition of COCs on ovarian androgen production. COCs also increase sex hormone-binding globulin (SHBG) concentrations. As SHBG binds and inactivates T, there is further suppression of the free T levels. The estrogen dose and progestin type of the COC do not influence the decline of total and free T, but both have a different effect on the levels of SHBG [8]. The bioavailability of adrenal androgens (e.g., dehydroepiandrosterone (DHEA) and its sulphate (DHEA-S)) is reduced as well, probably by inhibition of the adrenal androgen synthesis. In fact, COCs create a state of female androgen insufficiency [9]. In oophorectomised women, who have a sudden decline of androgens after surgery, the role of androgens have been shown to be critical for the maintenance of sexual function and psychological well-being [10]. Generally, there is a positive relationship between androgen levels and well-being in women [11]. However, sensitivity of women to changes in androgen levels is variable [12,13]. The question remains, whether the effect of hormonal contraception on mood disturbance is related to the induced changes in androgen levels, and whether androgen supplementation may result in improvement of mood disturbance in COC users. The purpose of this study was to evaluate the effect of concomitant DHEA treatment in healthy COC users who experience mood disturbances during COC-use only.

Methods

Study population

In Zuyderland Medical Centre Parkstad, Heerlen, Netherlands, six healthy COC users who complained of mood disturbances (e.g., irritation, depressive mood, anxiety, well-being) during COC-use, were selected by an open interview. Inclusion criteria were: use of COC for at least 3 months prior to screening, age 20–35 years, regular menstrual cycles (24–35 days) prior to last start of COC-use, body mass index 18–35 kg/m^2 and good physical and mental health. Exclusion criteria were: contraindications for

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COC-use, androgen therapy during the six months prior to screening, use of other than oral application routes of hormonal contraception during 3–6 months prior to screening, history of or current psychiatric disorder not related to COC-use, use of antidepressant medication prior to screening, lactation and/or pregnancy in the previous 6 months, concomitant medication that might interfere with metabolism of the contraceptive steroids or DHEA, and administration of any other investigational drug within 3 months before screening. The open interview was independently performed by two investigators (AW, FR) who are experienced in the field of gynaecology, using a questionnaire (Appendix A). There had to be a clear association between the start of mood complaints and start of COC-use, more complaints during COC intake and fewer complaints during the pill-free week.

The study was approved by an independent ethics review committee and was conducted in accordance with the Declaration of Helsinki and the ICH guideline for Good Clinical Practice. All subjects gave written informed consent. The study was registered at the Dutch trial registry (no. NTR1460).

Study design and procedures

After informed consent the subjects were included in a replicated, double-blind, placebo-controlled, single-case alternation design study over six treatment cycles [14]. The subjects received their own COC during six treatment cycles, with co-treatment of 50 mg DHEA during three treatment cycles and placebo during the other three cycles in an individualized random order. The pill-free period functioned as one week washout between each treatment cycle. The study design is depicted in Figure 1. Daily mood rating, the primary study parameter, was measured by a single item: 'In what kind of mood have you been in the past 24 h?' Subjects were asked to give a rate for their mood on a 5-point scale (1 meaning very negative and 5 meaning very positive), which was recorded in a diary. Subjects visited the clinic at the start of the pill-free period (on day 1 or 2 of the pill-free period) of each treatment cycle. During every treatment cycle, data were collected from all 28 days, but data obtained during the pill-free period were not used for the analysis. In this same diary, subjects had to report whether they had been taking the pills which were assigned to. Safety was evaluated by recording the objective and subjective side effects.

Study medication

DHEA was manufactured by Akzo Laboratories (Diosynth B.V., Oss, Netherlands) in accordance with Good Manufacturing Practices. The DHEA and placebo tablets were manufactured by Unither Pharmaceuticals (Le Haillan, France) and were identical in appearance. Blinded study medication i.e., neither the investigator nor the subject knew the treatment order and whether the co-treatment was DHEA or placebo, was packed per subject number according to a computer-generated randomisation list that was only known to an independent biostatistician. The treatment order had the constraint of maximally two consecutive administrations of the same treatment following the proper randomization schedule for alternating treatments designs [15].

Statistical analysis

For analysing the mean daily mood scores, a randomisation test for single-case experimental designs was carried out for each subject [16]. A randomisation test is a permutation test based on randomisation (random assignment) to test a null hypothesis about treatment effects in a randomised experiment. The difference between means was used as the test statistic, and this test statistic was computed for the experimental data and for all the other data divisions that were possible under the randomisation model. Those test statistics, including the one representing the obtained results, constitute the reference distribution for determining statistical significance. The proportion of test statistics that have values larger than or equal to the value for the experimentally obtained results is the *p* value. Treatment B (DHEA) was expected to be superior to treatment A (placebo). The analyses were performed using the Single-Case Randomization Tests package of the SCDA program in R [17,18]. The program also allows the calculation of a combined *p*-value, by considering several subjects

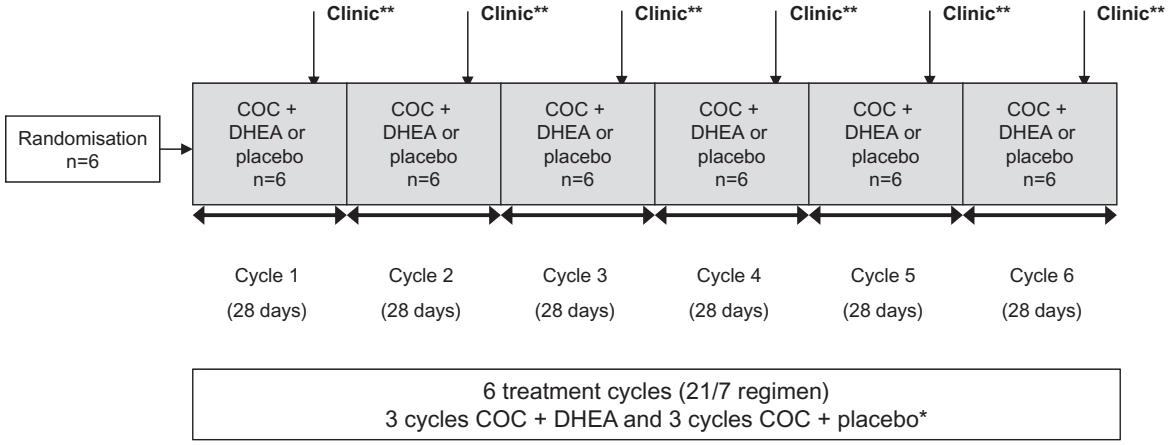

Figure 1. Design of the study. Six healthy Caucasian subjects received their own COC during six treatment cycles, with co-treatment of 50 mg DHEA during three treatment cycles and placebo during the other three cycles in an individualized random order and no more than two consecutive cycles with the same treatment. The pill-free period functioned as a one week washout between each treatment cycle.

simultaneously according to the type of pill used, in a meta-analysis using Edgington's additive method [16]. The level of statistical significance α was set at 5%.

Results

Demographic data and treatment-related information of the six participating COC users who complained of mood disturbances during COC-use only, are shown in Table 1. All six women were Caucasian and completed the study.

Table 2 shows the mean mood scores for each treatment [placebo (A) and DHEA (B)] for these six subjects. The p values for the alternation design randomisation tests on the raw data of the six healthy individuals varied between 0.21 and 1, indicating that the average daily mood ratings of the active treatment DHEA (B) are not statistically significantly larger than the average daily mood ratings of placebo (A). The combined p value of subjects 1, 5 and 6 using a DRSP-containing pill was $p = 0.97$, and of subjects 2, 3 and 4 using a LNG-containing pill $p = 0.65$, indicating no statistically significant treatment effect for any of the pill types (Table 2).

In total five adverse events were reported by three subjects; influenza-like illness (two; not related), seasonal allergy (one; note related), eczema on the face (one; possibly related) and headache (one; not related).

Discussion

Findings and interpretation

In this single-case alternation design study in six subjects who were selected for complaints of mood disturbances during COC-use only, no differences in daily and cycle mean mood ratings were found between DHEA and placebo supplementation to regular COC-use.

This finding is in contrast with our expectation that concomitant treatment with DHEA would result in improvement of mood disturbances during COC-use, but in accordance with another study [19]. The co-administration of DHEA did not cause side-effects.

Strengths and weaknesses of the study

Strengths of this study are its design, and the DHEA dosage used. The single-case alternation design is the ultimate form of verification in, for example, the individualization of treatment [14]. It is the best study design for demonstrating causality between agent and effect. However, it is possible that DHEA use during one cycle is too short to record improvement of mood disturbances during COC-use. A three-month DHEA vs. a three month placebo design might be interesting for future research to test this time relationship.

The study has some other weaknesses. Addition of 50 mg DHEA to a COC restores total T and free T completely [19]. However, in this study T measurements were not performed, so restoration of T levels could not be confirmed. In addition, the sensitivity of women to changes in androgen levels is variable [12], and the 50 mg dose of DHEA might be too low for these women [20]. The selection of subjects using a questionnaire was not optimal, as the basic mood score during regular COC-use was not very low in most subjects. Besides, mood is dependent on many psychosocial circumstances, making it difficult to assess the real influence of these variables in individuals. Possibly, future subject selection could be improved by performing the open interview by a psychologist using a validated

Table 1. Baseline characteristics and treatment-related information of the study population.

Subject number	Age (years)	BMI (kg/m^2)	Used COC	Duration of COC-use (years)	Number of COC switches
1	23	21.2	3 DRSP/20 EE	9	2
2	31	25.8	50-75-125 LNG/30-40-30 EE	3	1
3	21	24.3	150 LNG/30 EE	6	1
4	21	23.2	150 LNG/30 EE	6	2
5	22	20.5	3 DRSP/30 EE	5	5 (incl. Mirena®)
6	23	26.1	3 DRSP/30 EE	10	2 (incl. Mirena®)
Mean (SD)	23.5 (3.8)	23.5 (2.3)			

COC: combined oral contraceptive; DRSP: drospirenone; EE: ethinylestradiol; LNG: levonorgestrel.

Table 2. Mean mood score for each treatment [(A) placebo and (B) DHEA] per treatment cycle and per subject (a higher score means a better mood); mean mood score (SD) and difference (St diff) for the three means of each treatment (A–B) per subject; the p values on the mean data of the six healthy subjects; and the meta-analysis on the p values of subjects 1, 5 and 6 using a DRSP-containing pill, and subjects 2, 3 and 4 using an LNG-containing pill.

	Cycle						A–B		A < B
Subject number	1	2	3	4	5	6	Mean (SD)	Diff (St diff)	p Value[1]
1	4.00	3.90	4.10	3.76	3.86	3.95	3.97 (0.12)–3.89 (0.12)	0.08 (0.69)	0.79
Treatment	B	B	A	B	A	A			
2	3.29	3.90	3.38	3.95	3.43	3.67	3.84 (0.15)–3.37 (0.07)	0.47 (4.05)	1.00
Treatment	B	A	B	A	B	A			
3	3.24	2.81	3.05	4.05	2.76	2.38	3.02 (0.24)–3.08 (0.87)	−0.06 (−0.10)	0.50
Treatment	A	B	A	B	A	B			
4	2.71	3.14	3.48	2.90	3.29	3.33	2.98 (0.32)–3.30 (0.17)	−0.32 (−1.27)	0.21
Treatment	A	B	B	A	B	A			
5	3.57	3.29	3.43	3.67	3.38	3.48	3.51 (0.20)–3.43 (0.05)	0.08 (0.56)	0.71
Treatment	A	A	B	A	B	B			
6	3.14	3.19	3.57	3.05	3.62	3.33	3.46 (0.24)–3.17 (0.14)	0.29 (1.47)	0.93
Treatment	B	A	A	B	A	B			
$\Sigma_{(1,5,6)}$							3.65 (0.19)–3.50 (0.11)	0.15 (0.68)	0.97
$\Sigma_{(2,3,4)}$							3.28 (0.25)–3.25 (0.51)	0.03 (0.05)	0.65

A: placebo; B: DHEA; SD: standard deviation; St diff: standardized difference; 1: one-tailed test; $\Sigma_{(1,5,6)}$: meta-analysis subjects 1, 5 and 6; $\Sigma_{(2,3,4)}$: meta-analysis subjects 2, 3 and 4.

screening list, or by including only subjects who discontinued the COC for mood disturbances, or including subjects on androgen level data. The used 5-point scale was possibly not accurate enough to be able to discriminate between changes in mood scores. A 10-point scale would have been more optimal, or the use of a more specific rating list of mood disturbances such as irritation, depression, anxiety and well-being instead of rating only mood. This should also be done in the pill-free period.

Differences in results and conclusions from other studies

COCs reduce circulating free T levels by about 60% [8]. Testosterone deficiency is thought to be associated with a broad range of unwanted effects interfering with quality of life including mood changes (depression, irritation, moodiness), loss of energy, cognitive disturbances, sexual dysfunction, declining muscle strength and lowering of bone mass [9]. A certain group of women do report mood disturbances during COC-use, which could be related to the loss of T. Restoring androgen levels during COC-use by co-administration of DHEA could potentially diminish these mood disturbances. DHEA is the natural precursor hormone for androgens. Oral DHEA is metabolized into T, increases T levels dose dependently and restores T levels during COC-use. 50 mg DHEA increases T by about 1 nmol/L and has shown to be safe [20].

Relevance of the findings

In this study, DHEA supplementation did not result in improvement of mood disturbances in COC users. This could be due to incompleteness of the open interview to select the women for the study or to inadequacy of the 5-point scale to rate subtle changes in daily mood. On the other hand, it might be questioned that T insufficiency is indeed an important cause of mood disturbances during COC-use. Possibly, the loss of periovulatory ups and premenstrual downs during COC-use leading to mood equalization is a more relevant factor [21].

Unanswered questions and future research

The question whether the negative effect of hormonal contraception on mood is related to the induced changes in androgen levels, and whether androgen supplementation may result in improvement of mood disturbance, is unanswered in this study and still needs to be resolved, preferably in a study combining more specific mood disturbances and T assessments, and using a three-month DHEA vs. a three month placebo design.

Conclusions

In this single-case alternation design study in six healthy women who were selected for complaints of mood disturbances during COC-use only, concomitant treatment with DHEA for intermittent periods of 4 weeks did not result in improvement of mood disturbances related to COC-use, but had also no side-effects.

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Disclosure statement

Y. Z. is an employee and H.C.B. is CEO and shareholder of the company Pantarhei Bioscience (PRB), developing the Androgen Restored Contraception concept for contraception. PRB sponsored the study. F. R. serves *ad hoc* as investigator, medical advisor and lecturer of MSD, Bayer and other pharmaceutical companies manufacturing contraceptives. A. W., M. K. and P. O. have no conflicts of interest.

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Appendix A

Screening interview

Example of the screening interview in English (translation from Dutch version that was used during the study).

Two investigators, experienced in the field of gynaecology, will independently perform an open interview.

Objective: to determine if the mood disturbances of the subject are related or not related to the use of the oral contraceptive pill.

Answers to the following questions are required.

1. Living situation: Married/Living together/Relation/Single? How satisfied are you with your relationship?
2. What are your activities in daily life? How satisfied are you with your work/study?
3. Do you use any medication? If yes, which type of medication?
4. What do you understand exactly by mood disturbances/mood changes?
5. Have you ever been treated for depressive complaints? Have you ever visited a psychologist or psychiatrist?
6. Did you suffer from premenstrual syndrome (PMS) before starting the pill?
7. The pill:
   a. Why?
   b. Since when?
   c. Did you use several types? If yes, what was the reason for switching?
8. Why do you suppose a relationship between the use of the contraceptive pill and your mood disturbances?
   a. Describe your own mood disturbances.
   b. Did these complaints start immediately after starting pill use?
   c. Are these complaints worsening during any phase of your cycle?
   d. Did you already visit your family doctor or a gynaecologist for these mood disturbances?
   e. What influences do your mood disturbances have on the people in your own environment (partner, children, etc.)?
   f. Were there any events in your personal environment or at home that might explain your mood disturbances (the decease of a acquaintance, the break off of a relation, etc.)?
9. Are there any other changes in your well-being after starting pill use (energy/vitality; muscle strength/muscle volume; sexual desire; etc.)?