**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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18 ABSTRACT

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

21 **Methods** Six women with mood disturbances during COC-use only, received COC with co-
22 treatment of 50 mg dehydroepiandrosterone (DHEA) during 3 cycles and placebo during
23 another 3 cycles in an individualized random order. Daily mood rating was measured by a
24 single item: 'In what kind of mood have you been in the past 24 hours?' The results were
25 analysed using a randomisation test for single case experimental designs.

26 **Results** The p -values for the alternation design randomisation tests on the raw data of the six
27 healthy individuals varied between .21 and 1, indicating that the average daily mood ratings
28 of the active treatment DHEA are not statistically significantly larger than the average daily
29 mood ratings of placebo. The combined p -value of the subjects using a DRSP-containing pill
30 was .97, and of the subjects using a LNG-containing pill .65, indicating no statistically
31 significant treatment effect for any of the pill types.

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

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 The potential negative effects of COC on mood may cause discontinuation and switching.⁴ Young women with adverse psychological symptoms are at risk for perceived COC side effects and discontinuation.^{5,6} 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. Because SHBG binds and inactivate T, there is further suppression of the free T levels. The oestrogen 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.⁷ The bioavailability of adrenal androgens (e.g. dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S)) are reduced as well, probably by inhibition of the adrenal androgen synthesis. In fact, COCs create a state of female androgen insufficiency.⁸ 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.⁹ Generally, there is a positive relationship between androgen levels and well-being in women.¹⁰ However, sensitivity of women to changes in androgen levels is variable.^{11,12} 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, The 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 in-depth 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/m², and good physical and mental health. Exclusion criteria were: contraindications for COC-use, androgen therapy during the six months prior to screening, use of other than oral application routes of hormonal contraception during the 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 6 treatment cycles.¹³ The subjects

received their own COC during six treatment cycles, with co-treatment of 50 mg DHEA during 3 treatment cycles and placebo during the other 3 cycles in an individualized random order. The pill-free period functioned as a 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 hours?’. 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 they had been assigned to. Safety was evaluated by recording of objective and subjective side effects.

Study medication

DHEA was manufactured by Akzo Laboratories (Diosynth B.V., Oss, the 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.¹⁴

Statistical analysis

For analysing the mean daily mood scores, a randomisation test for single-case experimental designs was carried out for each subject.¹⁵ 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.^{16,17} The program also allows the calculation of a combined p -value, by considering several subjects simultaneously according to the type of pill used, in a meta-analysis using Edgington's additive method.¹⁵ 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 .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 $p = .97$, and of subjects 2, 3 and 4 using a LNG-containing pill $p = .65$, indicating no statistically significant treatment effect for any of the pill types (Table 2).

In total 5 adverse events were reported by 3 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.¹⁸ 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.¹³

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.¹⁸ 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,¹¹ and the 50 mg dose of DHEA might be too low for these women.¹⁹ 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 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 like irritation, depression, anxiety and well being instead of rating only mood. This should also be done in the pill-free week.

Differences in results and conclusions from other studies

COCs reduce circulating free T levels by about 60%.⁷ 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.⁸ 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.¹⁹

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 in-depth interview to select the women for the study or in 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.²⁰

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.

CONCLUSION

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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Declaration of interest:

YZ is employee and HCB is CEO and shareholder of the company Pantarhei Bioscience (PRB), developing the Androgen Restored Contraception concept for contraception. PRB sponsored the study. FR serves ad hoc as investigator, medical advisor and lecturer of MSD, Bayer, and other pharmaceutical companies manufacturing contraceptives. AW, PO, and MK have no conflicts of interest.

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REFERENCES

1. Poromaa IS, Segebladh B. Adverse mood symptoms with oral contraceptives. *Acta Obstet Gynecol Scand* 2012; 91:420-7.
2. Kahn LS, Halbreich U. Oral contraceptives and mood. *Expert Opin Pharmacother* 2001;2:1367-82.
3. Oinonen KA, Mazmanian D. To what extent do oral contraceptives influence mood and affect? *J Affect Disord* 2002;70:229-40.
4. Sanders SA, Graham CA, Bass JL, et al. A prospective study of the effects of oral contraceptives on sexuality and well-being and their relationship to discontinuation. *Contraception* 2001; 64:51-8.
5. Hall KS, White KO, Rickert VI, et al. Influence of depressed mood and psychological stress symptoms on perceived oral contraceptive side effects and discontinuation in young minority women. *Contraception* 2012;86:518-25.
6. Gingnell M, Engman J, Frick A, et al. Oral contraceptive use changes brain activity and mood in women with previous negative affect on the pill – A double-blinded, placebo-controlled randomized trial of a levonorgestrel-containing combined oral contraceptive. *Psychoneuroendocrinology* 2013;38:1133-44.
7. Zimmerman Y, Eijkemans MJC, Coelingh Bennink HJT, et al. The effect of combined oral contraception on testosterone levels in healthy women: a systematic review and meta-analysis. *Human Reprod Update* 2014;20:76-105.
8. Bachmann GA, Bancroft J, Braunstein G, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertil Steril* 2002;77:660-665.

- 234 9. Shifren J. Androgen deficiency in the oophorectomized woman. *Fertil Steril*
235 2002;77:S60-2.
- 236 10. Bancroft J. The endocrinology of sexual arousal. *J Endocrinology*
237 2005;186:411-27.
- 238 11. Elaut E, Buysse A, De Sutter P, et al. Relation of androgen receptor sensitivity
239 and mood to sexual desire in hormonal contraception users. *Contraception*
240 2012;85:470-9.
- 241 12. Graham C, Bancroft J, Doll H, et al. Does oral contraceptive-induced reduction
242 in free testosterone adversely affect the sexuality or mood of women?
243 *Psychoneuroendocrinology* 2007;32:246-55.
- 244 13. Vandenbroucke JP. The N-of-1 trial, the ideal study design that is underused.
245 *Ned Tijdschr Geneeskd* 2006;150:2794-5.
- 246 14. Onghena P, Edgington E. Randomization tests for restricted alternating
247 treatments designs. *Behaviour Research and Therapy* 1994;32:783-6.
- 248 15. Edgington ES, Onghena P. Randomization tests, fourth edition. New York:
249 Chapman and Hall/CRC. 2007.
- 250 16. Bulté I, Onghena P. An R package for single-case randomization tests.
251 *Behaviour Research Methods* 2008;40:467-78.
- 252 17. Bulté I, Onghena P. The Single-Case Data Analysis package: Analysing single-
253 case experiments with R software. *J Modern Applied Statistical Methods*
254 2013;12:450-78.
- 255 18. Zimmerman Y, Foidart JM, Pintiaux A, et al. Restoring testosterone levels by
256 adding dehydroepiandrosterone to a drospirenone containing combined oral
257 contraceptive: II. Clinical effects. *Contraception* 2015;91:134-42.

- 258 19. Legrain S, Girard L. Pharmacology and therapeutic effects of
259 dehydroepiandrosterone in older subjects. *Drugs and aging* 2007;20:949-67.
- 260 20. Silbergeld S, Brast N, Noble E. The menstrual cycle: A double-blind study of
261 symptoms, mood and behavior and biochemical variables using Enovid and
262 placebo. *Psychosomatic Medicine* 1971;33:411-28.
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LEGEND TO FIGURE 1

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 3 treatment cycles and placebo during the other 3 cycles in an individualized random order and no more than 2 consecutive cycles with the same treatment. The pill-free period functioned as a one week washout between each treatment cycle.

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

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

272 COC=combined oral contraception; DRSP=drospirenone; EE=ethinylestradiol; LNG=levonorgestrel

273 **Table 2.** Mean mood score for each treatment (placebo (A) and DHEA(B)) per treatment
 274 cycle and per subject (a higher score means a better mood); mean mood score (SD) and
 275 difference (St diff) for the three means of each treatment (A-B) per subject; the *p*-values on
 276 the mean data of the six healthy subjects; and the meta-analysis on the *p*-values of subjects 1,
 277 5 and 6 using a DRSP-containing pill, and subjects 2, 3 and 4 using a 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

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