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# Restoring testosterone levels by adding dehydroepiandrosterone to a drospirenone containing combined oral contraceptive: II. Clinical effects☆

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## Abstract

**Objectives:** Combined oral contraceptives (COCs) decrease androgen levels, including testosterone (T), which may be associated with sexual dysfunction and mood complaints in some women. We have shown that 'co-administration' of dehydroepiandrosterone (DHEA) to a drospirenone (DRSP)-containing COC restored total T levels to baseline and free T levels by 47%. Here we describe the effects on sexual function, mood and quality of life of such an intervention.

**Study design:** This was a randomized, double-blind, placebo-controlled study in 99 healthy COC starters. A COC containing 30 mcg ethinylestradiol (EE) and 3 mg DRSP was used for three cycles, followed by six cycles of the same COC combined with 50 mg/day DHEA or placebo. Subjects completed the Moos Menstrual Distress Questionnaire (MDQ), the McCoy Female Sexuality Questionnaire and the short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q). Safety and tolerability, including effects on skin, were evaluated.

**Results:** The addition of DHEA induced small but significant improvements compared to placebo in the MDQ score for autonomic reactions during the menstrual (−2.0 vs. 0.71; p=0.05) and the premenstrual phase (−3.1 vs. 2.9; p=0.01) and for behavior during the intermenstrual phase (−1.4 vs. 3.6; p=0.02). A significant difference was found in the MDQ score for arousal during the premenstrual phase in favor of placebo (−5.0 vs. 1.0; p=0.01). There were no statistically significant differences between groups for the MSFQ and Q-LES-Q scores. DHEA 'co-administration' resulted in an acceptable safety profile. DHEA negated the beneficial effect of the COC on acne according to the subjects' self-assessment.

**Conclusions:** 'Co-administration' with DHEA did not result in consistent improvements in sexual function, mood and quality of life indicators in women taking EE/DRSP. Retrospectively, the 50 mg dose of DHEA may be too low for this COC.

**Implications:** A well-balanced judgment of the clinical consequences of normalizing androgens during COC use may require complete normalization of free T.



*Keywords:* Androgens; Testosterone; DHEA; Mood; Sexual function

## 1. Introduction

The use of combined oral contraceptives (COCs) has been associated with negative effects on sexual function and mood in some women [1–9]. These side effects may result in discontinuation of COCs [7,10–12] and may have an adverse impact on quality of life [13]. Androgens, including testosterone (T), are believed to play a key role in sexual function and mood, and androgen replacement therapy, such as transdermal testosterone, has been shown to improve symptoms such as well-being, mood and sexual desire in pre- and postmenopausal women with sexual dysfunction [14–18].

COCs are known to reduce androgen levels, especially T [19,20], although no consistent effect on mood and sexual

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function has been observed [3,21–26]. However, reduced androgen levels may be an important factor contributing to COC-associated sexual dysfunction and mood complaints [27,28]. Therefore, by normalizing androgen levels, especially T, the negative effects of COCs on sexual function and mood could be ameliorated. Maintaining physiological androgen levels in women using a COC may be achieved by the addition of the natural human adrenal hormone dehydroepiandrosterone (DHEA); DHEA is partially metabolized into T [29–31] and could be incorporated into a COC pill because it is orally bioavailable [32].

We have reported that daily 'co-administration' of 50 mg DHEA to a drospirenone (DRSP)-containing COC significantly increased total T levels and restored baseline levels, whereas the biologically active free T levels were normalized by 47% only [20]. Here, we describe the effect of DHEA 'co-administration' on sexual function, mood and quality of life in new COC users without sexual function or mood complaints. In doing so, we wished to determine (a) whether COC use alone would result in unfavorable effects on sexual function, mood and/or quality of life and (b) whether six cycles of treatment with DHEA would have a favorable effect on sexual function, mood and/or quality of life compared to placebo.

## 2. Materials and methods

This was a randomized, double-blind, placebo-controlled study with a primary objective to assess the effects on androgen metabolism of the 'co-administration' of DHEA in subjects using a DRSP/ethinylestradiol (EE) COC compared to a control group of subjects receiving a DRSP/EE COC alone [20]. Here we report on the secondary study objectives, which included evaluating the effects of six treatment cycles with DHEA or placebo on sexual function, mood, menstrual symptoms and quality of life. General safety and acceptability, including skin characteristics of DHEA coadminstration, were also evaluated. Study population, design, procedures and medication are as described in the manuscript reporting the endocrine effects of this study [20]. Briefly, healthy females who were sexually active, aged between 18 and 35 years, and had a body mass index (BMI) between 18 and 35 kg/m$^2$ were enrolled. All participants must not have taken a hormonal contraceptive for at least 3 months prior to the start of the study medication.

### 2.1. Study design and procedures

Eligible participants were randomized to a 30 mcg EE and 3 mg DRSP COC with 'co-administration' of DHEA or placebo in a ratio of 1:1. The study consisted of a three-cycle run-in period with COC use alone followed by a six-cycle treatment period in which participants continued COC use in combination with either DHEA or placebo. Each treatment cycle consisted of 28 days. During all treatment cycles, participants took one tablet of the EE/DRSP COC from day 1 to day 21 followed by a pill-free period of 7 days. During the six-cycle treatment period, DHEA or placebo was used continuously, including during the pill-free period.

### 2.2. Assessment of sexual function, mood, menstrual cycle symptoms and quality of life

The clinical effect of COC use only and of DHEA 'co-administration' on mood, quality of life, menstrual cycle symptoms and sexual function was evaluated using the following validated self-administered questionnaires: the Moos Menstrual Distress Questionnaire (MDQ) [33,34], the McCoy Female Sexuality Questionnaire (MFSQ) [35] and the short form of the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) [36]. These three questionnaires were completed at study visits before starting COC use (baseline) and at the end of cycles 3 (end of run-in period), 4, 6 and 9 (the treatment period) or at premature discontinuation. In this manuscript, we have focused on reporting the change in scores from the end of the run-in period (cycle 3) to the end of the treatment period (cycle 9) in the DHEA group vs. placebo group, in accordance with the study objectives and statistical analysis plan. Assessments were performed during the pill-free period since most subjective complaints occur during that period of cyclic COC use [37,38].

#### 2.2.1. MDQ

The MDQ was used to assess menstrual cycle symptoms including those relating to mood. The questionnaire addresses 47 symptoms on a 6-point scale grouped in eight domains: Pain, Water retention, Autonomic reactions, Negative affect, Impaired concentration, Behavior change, Arousal and Control (Supplemental Table S1). Rating of menstrual cycle symptoms was completed by the subjects at each study visit for three phases of the cycle: most recent flow (menstrual phase), 4 days before flow (premenstrual phase) and remainder of cycle (intermenstrual phase). For all items, except the Arousal score, a lower score indicates more positive symptoms or reactions, while Arousal scores positively when it increases. A score of 50 is the standard (SD10).

#### 2.2.2. MFSQ

The MFSQ questionnaire is designed to measure major aspects of female sexuality and particularly those aspects of female sexuality likely to be affected by changes in sex hormone levels. The MFSQ assesses sexual functioning using 19 items on a 7-point scale, where a higher score means a better result (higher quality of life). It is divided into 6 domains: Global score, Sexual interest, Satisfaction, Vaginal lubrication, Orgasm and Sexual partner.

#### 2.2.3. Q-LES-Q

The Q-LES-Q questionnaire is a self-reported measure designed to easily obtain sensitive measures of the degree of enjoyment and satisfaction experienced by subjects in various areas of daily functioning. It consists of 16 items