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Original research article

Maintaining physiologic testosterone levels during combined oral contraceptives by adding dehydroepiandrosterone: II. Effects on sexual function. A phase II randomized, double-blind, placebo-controlled study☆,☆☆,★

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ABSTRACT

Objective: The objective was to evaluate the effect of combined oral contraceptives (OCs) on sexual function, either alone or together with dehydroepiandrosterone (DHEA).
Study design: An exploratory randomized, double-blind, placebo-controlled, comparative, crossover study was conducted in 81 OC users. Subjects discontinued their OC for one cycle before being randomized for 10 cycles to a 30-mcg ethinyl estradiol (EE)/levonorgestrel (LNG) OC or a 30-mcg EE/drospirenone (DRSP) OC, along with daily use of 50 mg dehydroepiandrosterone (DHEA) or placebo during five OC cycles before crossing over from DHEA to placebo or the reverse for another five cycles. First, the effect on sexual function of five OC cycles + placebo was compared to baseline. Then, the effect of five OC cycles + DHEA was compared to the OC + placebo. Results regarding endocrine changes have been published separately. Primary efficacy outcomes of the current study were genital response (measured by vaginal pulse amplitude [VPA]) and sexual feelings (measured by the subjective self-assessment questionnaire [SSAQ]) to self-induced erotic fantasy and visual sexual stimuli in a laboratory setting and measures of desire and arousability using a sexual function diary (SFD). Secondary efficacy outcomes were the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale Revised.
Results: Eighty-one women were enrolled, and 74 women completed the study. Five cycles of OC + placebo resulted in a significant decline compared to baseline of four out of six SFD self-ratings of sexual desire and arousability with both OCs. The LNG OC also resulted in significant declines in the FSFI scores (baseline vs. LNG OC + placebo: total score, 28.7±3.7 vs. 25.6±7.4; arousal, 5.0±0.7 vs. 4.5±1.4; lubrication, 5.2±0.9 vs. 4.6±1.7; pain, 4.9±0.9 vs. 4.5±1.4), but no changes were observed using the DRSP OC. In the laboratory setting, five cycles of OC + DHEA showed no significant differences with placebo except for a significant increase in genital sensations (SSAQ) during erotic fantasy (OC + placebo vs. OC + DHEA: 3.3±1.4 vs. 3.6±1.5; $p<.05$). No significant changes were observed for genital response (VPA) and the other two variables of the SSAQ assessed after visual erotic stimulus exposure. Using the SFD, 5 out of 10 variables showed a significant improvement with DHEA. Partner's initiative was rejected less often with OC + DHEA compared to placebo (OC + placebo vs. OC + DHEA: 1.1±1.5 vs. 0.8±1.0; $p<.05$). Women with free testosterone levels in the upper quartile during DHEA co-administration showed significantly better effects on sexual arousal and desire compared to the three lower quartiles (lower vs. upper quartiles: sexual arousability: 25.0±19.8 vs. 41.2±29.0; sexual desire: 5.6±3.7 vs. 9.6±8.0; desire for sex with partner: 4.9±3.1 vs. 8.6±7.4; number of sex fantasies: 3.0±3.2 vs. 5.5±4.4; all $p<.05$).
Conclusions: In this exploratory study, OC use was associated with decreases in some measures of sexual

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functioning, whereas others remained unchanged. Maintaining or restoring physiological testosterone concentrations by the co-administration of DHEA to the OC may prevent these effects on sexuality, particularly in women with relatively high but physiologic levels of free testosterone during DHEA co-administration.
Implications: The results of this exploratory study warrant further testing of the hypothesis that restoration and/or preservation of physiologic testosterone levels during OC use by co-administration of DHEA has favorable effects on those aspects of sexual function compromised by OCs.

1. Introduction

Most women using a combined oral contraceptive (OC) experience a loss of androgens, especially testosterone [1]. Several studies have found a relationship between androgens and sexual function in women, in particular with sexual desire and arousability [2–7], whereas others did not [8–10]. Although it seems plausible that reduced androgen levels may contribute to impaired sexual function experienced by some OC users [11,12], reported effects of OCs on sexual function vary widely [13–18]. For some women, androgens may be more important for sexual functioning compared to others [12], and such women may be more vulnerable to sexual side effects of OCs [19].

Physiological levels of testosterone can be maintained in OC users by adding the human adrenal hormone dehydroepiandrosterone (DHEA), which is partly metabolized to testosterone [20–22]. Since DHEA is orally bioavailable, it is suitable for incorporation in an OC formulation [23]. A recent study in healthy women on the endocrine and clinical effects of adding DHEA to a drospirenone (DRSP)-containing OC reports the restoration of total testosterone to baseline levels, but only a 47% increase of free testosterone levels due to binding of testosterone to the concomitantly risen sex hormone-binding hormone (SHBG) [24]. In the same study, co-administration of DHEA compared to placebo significantly improved mood-related symptoms of menstrual distress (autonomic reactions and behavior) and showed a nonsignificant trend towards improvement in some measures of sexual function [24]. All significant differences found in this study were in favor of DHEA except for arousal (i.e., irritation) in the premenstrual phase which was less with placebo.

In a companion paper [25], we report that five cycles of ethinyl estradiol (EE)/levonorgestrel (LNG) or EE/DRSP significantly reduced total testosterone (54.5% and 11.3%, respectively) and free testosterone (66.8% and 75.6% respectively). Adding DHEA, but not placebo, restored free testosterone to baseline levels in both OC groups. In the current study, OC users discontinued their OC for one cycle and were thereafter randomly assigned to two different OCs, either EE/LNG or EE/DRSP, for 10 cycles. In addition, the subjects were randomized to concomitant daily use of 50 mg DHEA or placebo for five OC cycles and crossed over thereafter to the other co-treatment for another five cycles.

The objectives of this exploratory study were threefold: (a) to investigate the effects of OC use on sexual function by comparing baseline to five cycles of OC + placebo treatment, (b) to investigate the effect of daily co-administration of 50 mg DHEA compared to placebo on genital and subjective sexual response in a laboratory setting as well as in the home setting using diaries and (c) to investigate the relationship between changes in free testosterone with DHEA and sexual function.

2. Materials and methods

2.1. Study population

Eligible subjects were 20–35-year-old contraceptive pill users who were in a stable, satisfactory, heterosexual relationship; had a body mass index (BMI) of 18–35 kg/m^2 and total testosterone levels below 5 nmol/L; and were willing to interrupt OC use for one cycle. Other inclusion criteria were satisfaction with current relationship (General Marital Satisfaction scale score <20 of the Maudsley Marital Questionnaire [26]) and healthy psychological functioning (Symptom Check List-90 Depression scale score <28 and Anxiety scale score <18 [27]). The presence of sexual problems within the context of a satisfactory relationship and healthy psychological functioning (verified with a sexual history taken by an experienced sexologist) was not an exclusion criterion, such that both women with and without sexual problems could enter the trial. Acne was not an exclusion criterion.

The study was approved by the Medical Ethics Committee of the Academic Medical Center (Amsterdam, the Netherlands) and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. All participants provided written informed consent. The study was registered at ISRCTN (no. ISRCTN03247616).

2.2. Study design and procedures

This randomized, double-blind, placebo-controlled, crossover study was conducted at the Academic Medical Center (Amsterdam, the Netherlands). In accordance with study protocol, each subject discontinued her contraceptive pill for one cycle (the baseline cycle period; Fig. 1). After the baseline cycle, participants were randomly assigned to one of two OCs for 10 cycles: either 30 mcg EE+3 mg DRSP (Yasmin; Bayer Healthcare, Berlin, Germany) or 30 mcg EE+30 mcg LNG (Microgynon; Bayer Healthcare). In addition, participants received five-cycle treatment with DHEA or placebo (treatment period 1), assigned randomly, and then crossed over to the other treatment for the next five cycles (treatment period 2). DHEA or placebo was continued during the 7-day OC-free period. Participants were aware of which OC they received through randomization. The participants and investigators were blinded to the order in which participants received DHEA or placebo.

The DHEA and placebo tablets, manufactured by Unither Pharmaceuticals (Le Haillan, France), were identical in appearance. Blinded study medication was packed per subject number by ACE Pharmaceuticals (Zeewolde, the Netherlands) according to a computer-generated randomization list.

2.3. Primary efficacy outcomes

2.3.1. Genital and subjective sexual response to erotic stimuli

Genital sexual arousal (by vaginal pulse amplitude [VPA]) and subjective experience of sexual feelings (by subjective self-assessment questionnaire [SSAQ]) in response to erotic stimuli were measured in a laboratory session that took place between days 14 and 17 of the baseline cycle and of the fifth cycle of each treatment period. Women were exposed to four erotic stimuli in sequence: a 3-min self-induced erotic fantasy (SEF), a 5-min visual sexual stimulus (VSS) depicting heterosexual foreplay, another SEF followed by VSS depicting cunnilingus and vaginal intercourse. VSS was taken from female-initiated, female-centered erotic films. To avoid habituation resulting from repeated exposure to the same sexual stimulus, different but comparable stimuli were used and randomly allocated to laboratory sessions. Genital response was continuously measured as VPA using vaginal photoplethysmography [28]. Following exposure to each of the four erotic stimuli, subjects filled out three scales of the SSAQ [29] to measure the subjective response: sexual arousal, genital sensations and sensuality.

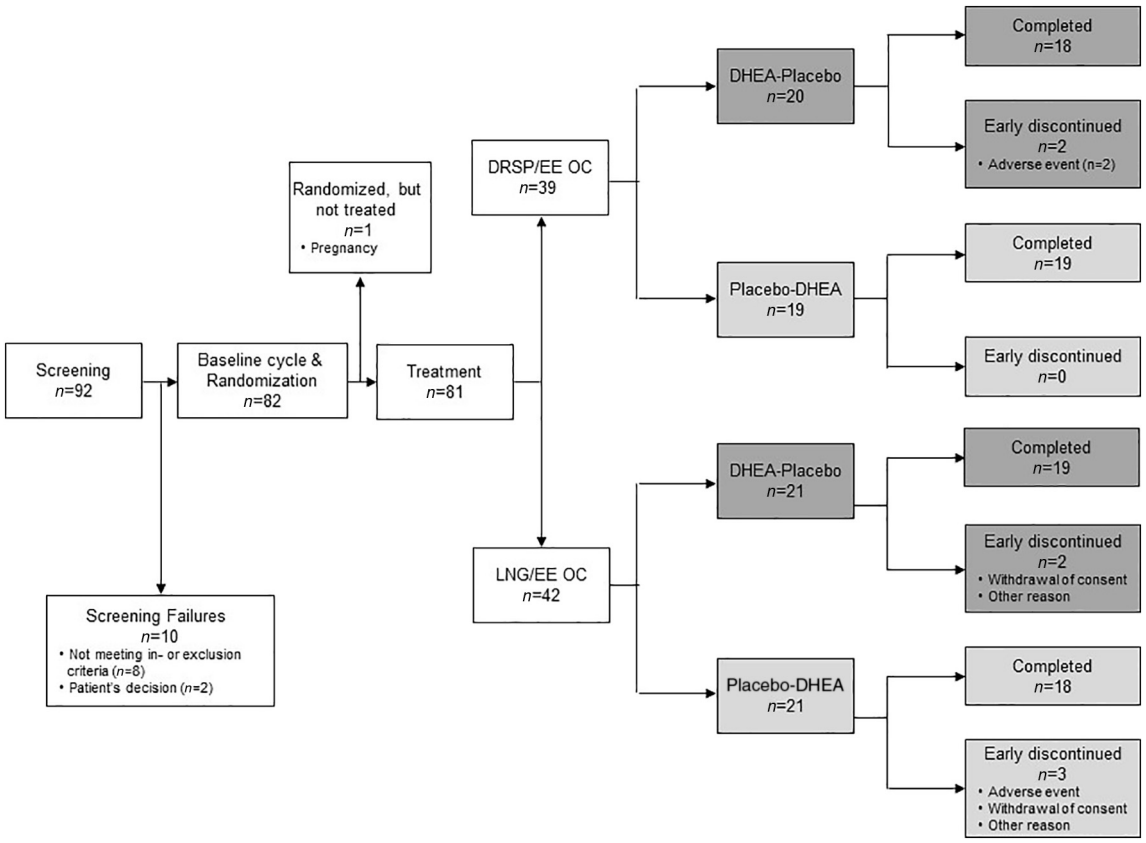

Fig. 1. Study design and subject disposition. Baseline refers to 1 month with no OC use prior to the treatment phase of the study.

2.3.2. Sexual desire and arousability as assessed by the Sexual Function Diary (SFD)

The SFD was used to assess sexual function at home. The diary was completed daily on days 8 to 14 of the baseline cycle and on days 8 to 14 of the last two cycles of both treatment periods. The SFD provides six self-ratings of frequency of sexual feelings (intimacy, sexual arousability, fantasy, arousal, sexual desire, desire for sex with partner), and four sexual behavior frequency ratings (masturbation, partner sex, taking initiative and rejecting partner's initiative). Scores were converted to mean scores per treatment period. Frequency items were reported as total scores per week [30].

2.4. Secondary efficacy outcomes

Two validated Dutch translations of questionnaires assessing sexual function, the Female Sexual Function Index (FSFI) and the Female Sexual Distress Scale-Revised (FSDS-R), were completed at baseline and prior to each laboratory session [31]. FSFI measures sexual function on six domains: desire, arousal, lubrication, orgasm, satisfaction and pain. An FSDS-R total score ≥15 combined with an FSFI total score <26.55 is indicative of sexual dysfunction [32,33].

2.5. Safety and tolerability

Adverse events, serious adverse events and pregnancies were assessed throughout the study. Vital signs, body weight, physical examination and laboratory tests (hematology and biochemistry) were assessed at baseline and follow-up (7–14 days after last treatment). Androgen-related skin symptoms such as acne, seborrhea and hirsutism were judged independently by investigator and the subject at each study visit using a score of none, mild, moderate or severe.

2.6. Statistical analysis

An effect on VPA during erotic fantasy and on SFD items for the within-subject comparison between DHEA and placebo was used for the calculation of sample size [30]. A minimum of 36 subjects was required with a chosen α-value of 0.05, a power of 80% and an effect size of 0.50 [34]. As two different OCs (EE/DRSP and EE/LNG) were used, 72 evaluable subjects were needed.

Data were analyzed on a per-protocol approach, including all subjects who completed both treatment phases. As there were no missing data for the laboratory sessions and very few for the diary and questionnaire measures, no missing-values imputation took place. Unless indicated otherwise, all summary results are expressed as mean ± SD. Within- and between-subject effects were tested with repeated-measures analyses of variance, with treatment (DHEA vs. placebo) as the within-subject factor and OC type (LNG vs. DRSP) and treatment order as between-subject factors. Scores were log-transformed to normalize the distribution of the variables when appropriate. Analyses were performed using IBM SPSS statistics 21.0.

3. Results

3.1. Study population characteristics

Study disposition, baseline demographic characteristics and endocrine data, including levels of total and free testosterone and SHBG, are summarized in our companion paper [25]. EE/DRSP and EE/LNG

groups were similar with respect to age, BMI, ethnicity, type of OC used prior to the study and endocrine parameters.

3.2. OC + placebo versus baseline

No significant differences were found for the laboratory measures (VPA and SSAQ). Compared to baseline, four out of six SFD self-ratings were significantly lower with both OCs (all p<.05; Fig. 2). The FSFI total score (p<.02) and three out of six FSFI domains (arousal [p<.05], lubrication [p<.01] and pain [p<.02]) were worse with EE/LNG compared to baseline, but not with EE/DRSP (Fig. 3). With an OC, 33.3% of women had an FSFI total score below 26.55, the established cutoff value for sexual dysfunction, compared to 24.4% at baseline (p<.05). The results of the FSDS-R questionnaire did not show any significant changes.

3.3. OC + DHEA versus OC + placebo

No significant differences were found between DHEA and placebo for VPA (data not shown). With DHEA, genital sensations (SSAQ) increased during erotic fantasy in the laboratory session (Table 1).

Sexual encounters initiated by the partner measured by the SFD were rejected less often when women were taking OC + DHEA (0.8±1.01 times/week) compared to when taking OC + placebo (1.1±1.5 times/week; p<.05; Fig. 4). Number of rejections is one of the four sexual behavior indices of the diary. Some additional significant interactions related to the crossover design were observed for the SFD data, most likely resulting from small carryover effects without relevance for the treatment effects under study. No significant changes were observed in the secondary parameters FSFI and FSDS-R (data not shown).

3.4. Associations between free testosterone levels and sexuality measures

Women with the highest quartile (75–100) of free testosterone levels during DHEA treatment were compared to those with free testosterone levels in the lower three quartiles (0–75). This analysis revealed that the following four SFD self-ratings of arousability and desire were significantly higher in women with free testosterone levels in the highest physiological quartile: sexual arousability: 25.0±19.8 vs. 41.2±29.0, sexual desire: 5.6±3.7 vs. 9.6±8.0, desire for sex with partner: 4.9±3.1 vs. 8.6 ±7.4 and number of sex fantasies: 3.0±3.2 vs. 5.5±4.4 (all p<.05; Fig. 5).

3.5. Safety and tolerability

For the analyses of the safety data, data from all subjects who took at least one dose of study medication were included. Both OC and DHEA use were well tolerated. No clinically relevant changes were noted for

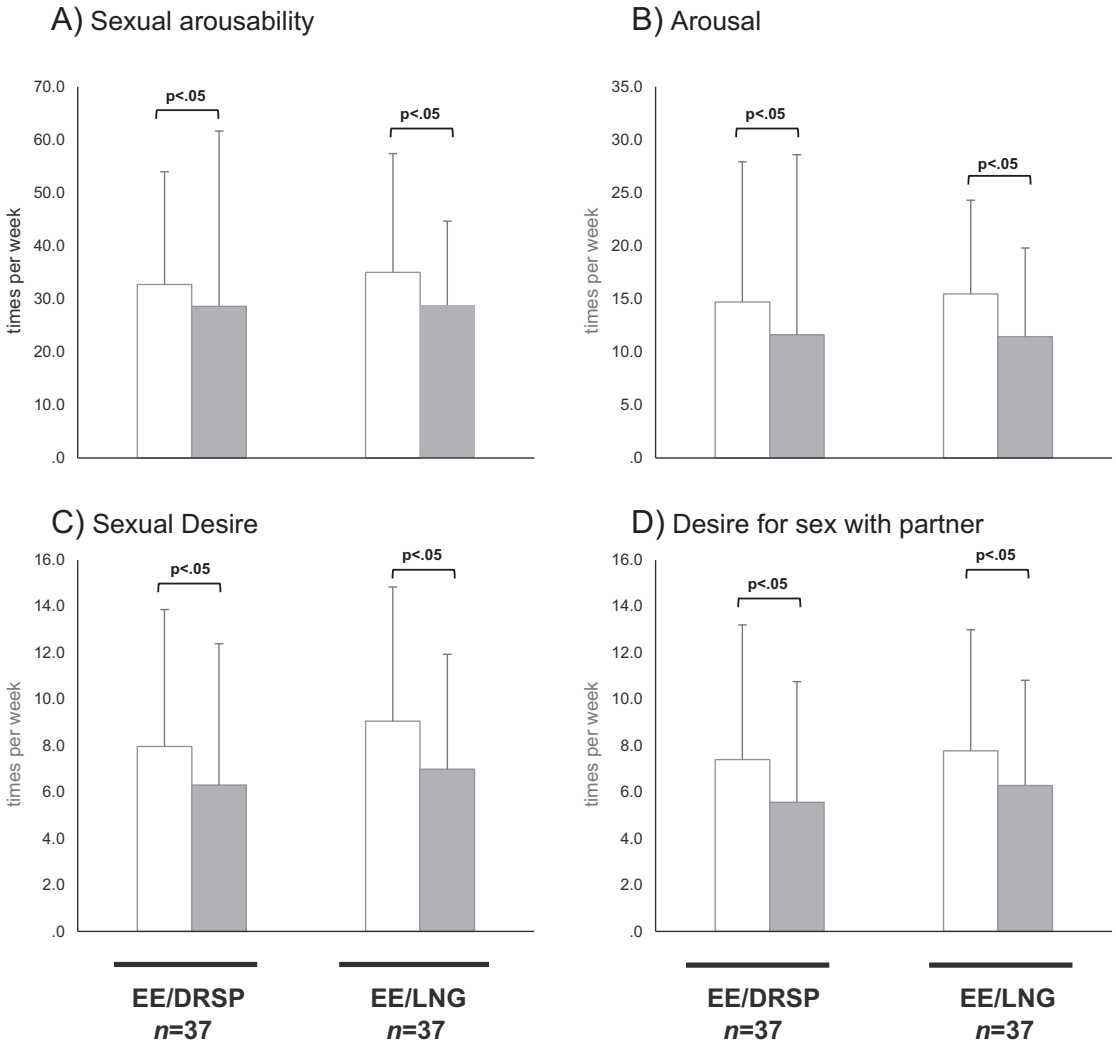

Fig. 2. Scores for the SFD self-ratings of *sexual arousability* (A), *arousal* (B), *sexual desire* (C) and *desire for sex with partner* (D), measured at baseline (no OC; white columns) and after five cycles of EE/DRSP or EE/LNG OC with placebo (light gray columns). (A) Sexual arousability is the weekly frequency of sexual thoughts, sensitivity to sexual stimuli and feelings of sexual attraction (four items); (B) arousal is the weekly frequency of feelings of sexual arousal (two items); (C) sexual desire is the weekly frequency of desire for sex (one item); (D) desire for sex with partner is the weekly frequency of desire for sex with own partner (one item).

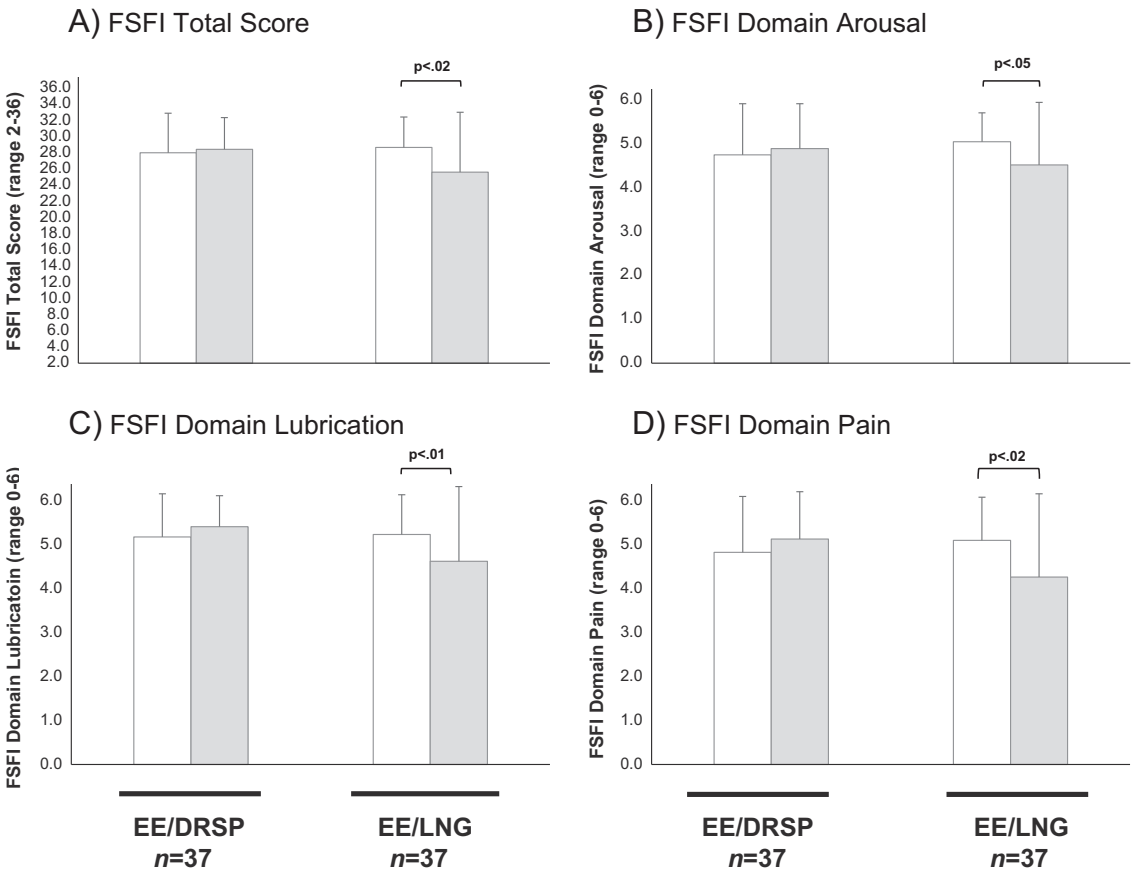

Fig. 3. The FSFI total score (A) and FSFI domains *arousal* (B), *lubrication* (C) and *pain* (D), measured at baseline (no OC; white columns) and after five cycles of EE/DRSP or EE/LNG OC with placebo (light gray columns).

vital signs, body weight or laboratory parameters. The effects on lipid parameters and glucose are shown in Supplemental Table 1. DHEA co-administration itself had no effects on lipids and glucose.

The results of judgement of androgen-related skin symptoms by the investigator and the OC user herself are summarized in Supplemental Table 2. Six subjects (five during DHEA and one during placebo) reported severe acne, in two cases combined with seborrhea (both during DHEA). For one of these cases, acne was reported as adverse event while taking placebo, and this subject discontinued study treatment early for this reason. No severe acne was reported according to the investigator's assessment. All of the women reporting severe acne also reported mild or moderate skin problems before starting use of study medication or during placebo. One subject had a total testosterone above the upper limit with DHEA without clinical signs of hyperandrogenicity, and she discontinued the study.

4. Discussion

The data from this exploratory study testing the effect of OCs only and of OCs combined with DHEA on several at home and laboratory indices of sexual function demonstrate that (a) OCs affect some aspects of sexuality, (b) adding DHEA to an OC repairs some of those affected aspects of sexual function and (c) the effects of DHEA co-administration are observed especially in women with free testosterone levels in the highest physiological range.

Table 1
Sexual feelings as measured by the SSAQ (three scales) at baseline and after five cycles of EE/DRSP or EE/LNG COC with 50 mg/d DHEA or placebo.

Parameter	*n*	Erotic stimulus	Baseline (no OC)	OC + placebo	OC + DHEA
SSAQ scores (range 1–7)					
	73–74	Fantasy 1	3.8±1.4	3.4±1.3	3.6±1.3
Sexual		Fantasy 2	4.1±1.5	4.0±1.3	4.0±1.4
arousal		Film 1	5.1±1.3	5.0±1.3	4.9±1.3
		Film 2	5.1±1.4	4.9±1.4	5.0±1.4
	73–74	Fantasy 1	3.7±1.5	3.3±1.4	**3.6±1.5***
Genital		Fantasy 2	3.9±1.5	3.8±1.5	3.9±1.4
sensations		Film 1	5.0±1.3	4.9±1.4	5.0±1.2
		Film 2	5.0±1.3	4.9±1.4	5.0±1.4
	73–74	Fantasy 1	3.9±1.1	3.9±1.1	4.0±1.2
		Fantasy 2	4.3±1.2	4.2±1.1	4.4±1.1
Sensuality		Film 1	4.3±1.0	4.4±1.0	4.4±1.0
		Film 2	4.3±1.1	4.4±1.1	4.5±1.2

Data expressed as mean ± standard deviation.
* p<.05 (DHEA versus placebo).

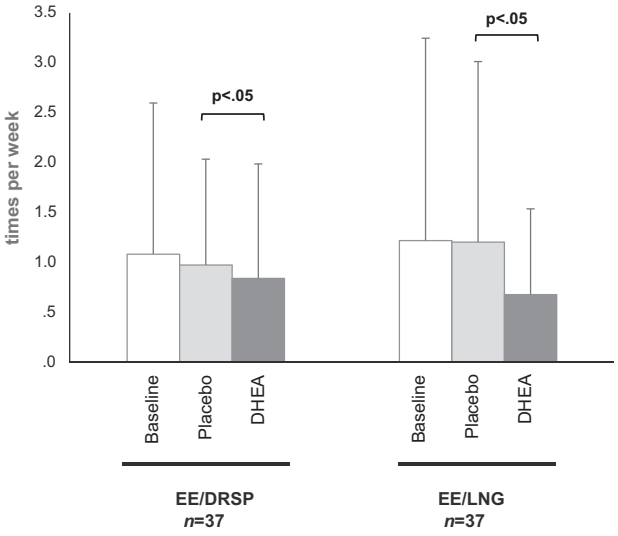

Fig. 4. Scores for the SFD question "How often did you reject a sexual initiative by your partner?" measured at baseline (no OC; white columns) and after five cycles of EE/DRSP or EE/LNG OC with placebo (light gray columns) or DHEA (dark gray columns). p values indicated for effect DHEA (placebo vs. DHEA; comparison with end of treatment values).

As mentioned earlier, no consensus exists whether or not OCs affect sexual function [26–29]. In the present study, significant decreases are observed in self-ratings of sexual arousability, desire and desire for sex with a partner with both OCs relative to baseline (no OC). These aspects of sexual function are considered to be androgen dependent [2–6] and have been found to decrease by the use of OCs in several other studies too [7,35–39]. Non-androgen-dependent sexual behavior variables and genital and subjective responses to sexual stimuli in a laboratory setting are not affected. Decreases in sexual function as measured with the FSFI are only observed in women using the LNG OC and not with the DRSP OC, which is somewhat surprising since LNG is believed to be more androgenic compared to DRSP. Altogether, the OC-only data of the current study are in line with previous studies demonstrating a negative impact of OCs on some measures of sexuality. We hypothesize that this may be related to the suppression of (free) testosterone by OCs [1,40–42].

The addition of 50 mg/d DHEA did not result in achieving the primary endpoint set at an effect of 0.5 with VPA or with the SFD. However, small significantly positive effects were found on two aspects of sexual function with both OCs: one in the laboratory setting (improved genital sensations to self-induced sexual fantasy) and one when using the SFD at home (decreased rejection of partner's initiative, which is an aspect of sexual arousability). The latter effect seemed stronger with the LNG compared to the DRSP OC. This is compatible with the finding that the LNG OC had somewhat more negative effects on sexuality relative to no OC use than the DRSP OC.

This study has some limitations. First, women who volunteer for studies involving intravaginal measurements have been found to be sexually more experienced and to be less concerned about sexual performance than nonvolunteers [43] and may therefore be different from the regular OC user. The women participating in this study were also not selected for having problems with sexual function while using an OC, but for this concept, it would be interesting to perform a study in this type of women. Second, this study employed many comparisons

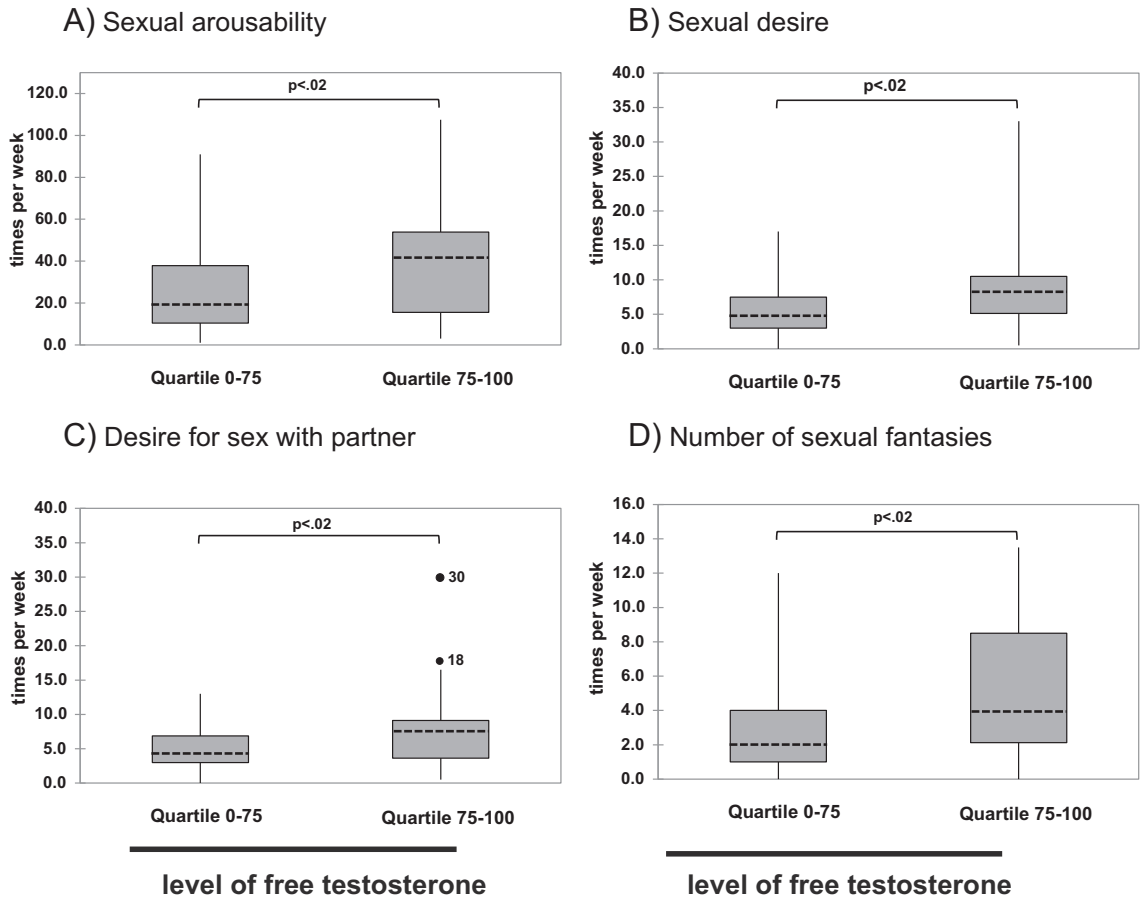

Fig. 5. Scores for the SFD self-ratings of *sexual arousability score* (A), *sexual desire* (B), *desire for sex with partner* (C) and *number of sexual fantasies* (D) by women's free testosterone response (low: quartile 0–75 and high: quartile 75–100) after five cycles of EE/DRSP or EE/LNG OC with DHEA. p values indicated for the comparison quartile 0–75 vs. quartile 75–100 (at end of DHEA treatment).

across measures and conditions. Therefore, findings could be due to chance. Finally, the broad range of baseline physiological total and free testosterone levels as reported previously [25] may also be a limitation of the study because women with (very) low baseline testosterone levels are not expected to develop symptoms due to a small further decrease of testosterone levels by using an OC. On the contrary, women with the highest physiological testosterone levels at baseline will experience the strongest decreases and are expected to be most at risk of adverse effects on sexual function. These women may benefit most of restoration of testosterone by DHEA. This is confirmed by our finding of a significant relationship between upper quartile free testosterone levels during DHEA use and improved self-ratings of sexual arousability, desire and fantasy.

In the present study, we have observed that women with androgenic skin symptoms such as acne may lose the beneficial skin effects of testosterone suppression by OCs. More cases of serious acne were reported with DHEA. These women also reported mild to moderate skin problems before starting the study medication or during placebo. In all these cases, the participants appeared to have been randomized to an LNG OC, known to be less favorable for acne. Therefore, women with androgenic skin symptoms may not benefit from DHEA co-administration and may not be suitable for treatment with an androgen-restoring OC.

In summary, this is a classical endocrine study, first removing a hormone (i.e., testosterone by the use of OCs) then observing the clinical implications (negative effects on sexual function) and thereafter substituting the hormone (DHEA administration), documenting restoration of (free) testosterone and investigating whether the observed clinical consequences are repaired (improvement of sexual function). No doubt much larger studies in appropriately selected patient populations are needed to confirm and extend the efficacy and safety of the androgen restored contraception concept, which may in principle be suitable for all combined oral contraceptives.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.contraception.2018.02.014.

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