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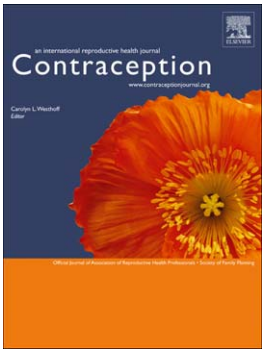

Restoring testosterone levels by adding dehydroepiandrosterone to a drospirenone containing combined oral contraceptive: II Clinical effects

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

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Conflict of interest

YZ is an employee of Pantarhei Bioscience (PRB), the company developing the Androgen Restored Contraceptive concept for contraception. JMF has no conflict of interest in the course of this study. AP shares expertise as a lecturer, member of advisory boards, and/or consultant, with Bayer, Amgen, Gedeon Richter and Teva/Theramex, without personal gain. JMM has nothing to declare. KC has nothing to declare. BF has received fees and grant support from the following companies (in alphabetic order); Andromed, Ardana, Euroscreen, Ferring, Genovum, Merck (MSD), Merck Serono, Organon, Ovascience, Pantharei Bioscience, PregLem, Schering, Schering Plough, Serono, Uteron Pharma, Watson Pharmaceuticals and Wyeth. HCB is the CEO and a shareholder of PRB.
After publication of the paper, PRB will make the clinical study report available upon request. The authors alone are responsible for the content and the writing of the paper.

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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 µg ethinylestradiol (EE) and 3 mg DRSP was used for 3 cycles, followed by 6 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 (MFSQ) 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 pre-menstrual phase (-3.1 vs 2.9; *P*=0.01); and for Behavior during the inter-menstrual phase (-1.4 vs 3.6; *P*=0.02). A significant difference was found in the MDQ score for arousal during the pre-menstrual 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.

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 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 (i) whether COC use alone would result in unfavorable effects on sexual function,

mood and/or quality of life and (ii) whether 6 cycles of treatment with DHEA would have a favorable effect on sexual function, mood and/or quality of life compared to placebo.

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 drospirenone-ethinylestradiol (DRSP/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 6 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 co-adminstration 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.

Study design and procedures

Eligible participants were randomized to a 30 µg EE and 3 mg DRSP COC with co-administration of DHEA or placebo in a ratio of 1:1. The study consisted of a 3 cycle run-in period with COC use alone, followed by a 6 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 6-cycle

treatment period, DHEA or placebo was used continuously, including during the pill-free period.

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].

MDQ

The MDQ was used to assess menstrual cycle symptoms including those relating to sexual function and mood. The questionnaire addresses 47 symptoms on a six-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); four days before flow (pre-menstrual phase); remainder of cycle (inter-menstrual 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).

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.

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 on a 5-point scale; a higher score indicates a better result i.e. greater enjoyment or satisfaction (1 = very poor to 5 = very good). Subjects completed this questionnaire at the end of each week during cycles 3 (end of run-in period), 4, 6 and 9.

Safety and tolerability

Safety and tolerability was assessed during all study visits and included vital signs, body weight, physical examination, safety laboratory tests (hematology and biochemistry) and adverse events. Any clinically relevant findings were recorded as adverse events. Skin characteristics related to androgens such as acne, seborrhea and hirsutism were judged independently by both the investigator and the participant at each study visit using a score of none, mild, moderate or severe.

Statistical analysis

The study was not powered to find statistical differences for the questionnaires related to clinical outcomes. The main comparison was the change in scores from the end of the run-in period (Cycle 3) to the end of treatment (Cycle 9) in the DHEA group vs placebo to determine if any changes in sexual function and/or mood caused by COC use would improve after addition of DHEA (i.e. after restoration of the T levels). Changes from baseline to the end of run-in period (Cycle 3) were also tested to determine the effect of COC use alone. For the main comparison, an analysis of covariance on log transformed values with baseline as a covariate was performed. The non-parametric method Kruskal-Wallis one-way analysis of variance was used to test whether there were differences in skin characteristics between groups. Results were considered to be significant at the 5% level ($P < 0.05$). All calculations were carried out using SAS (Version 9.1 for Windows) and S-PLUS (Version 7.0) statistical packages.

Results

The effect of DHEA co-administration on endocrine parameters are reported elsewhere [20]. The baseline demographic characteristics of the study population were comparable between groups for age, body mass index and ethnic origin [20].

Sexual function, mood, menstrual cycle symptoms and quality of life

MDQ

After 3 cycles of COC use only MDQ domain scores generally improved (<50) for the menstrual (most recent flow) and pre-menstrual phases (4 days before most recent flow), except for Autonomic reactions during the menstrual phase and for Arousal (Supplemental

Table S2). Statistically significant improvements at the 0.05 level were found for Impaired concentration during all phases, for Pain during the menstrual phase and for Control during the inter-menstrual phase (remainder of cycle) (Supplemental Table S2). The domain Arousal worsened during COC for all 3 phases, with a statistically significant difference for the inter-menstrual phase only ($P < 0.001$) (Supplemental Table S2).

During co-administration of DHEA or placebo, a mixed effect was seen for Autonomic reactions. At the end of Cycle 9, the change (Cycle 3- Cycle 9) in the domain score for Autonomic reactions was statistically significantly better in the DHEA group compared to the placebo group for the menstrual ($P = 0.05$) and pre-menstrual phases ($P = 0.01$) (Table 1; Figure 1). The change in the domain for Behavior was also significantly improved in the inter-menstrual phase compared to placebo ($P = 0.02$) (Table 1; Figure 1). A significant difference was found for Arousal during the pre-menstrual phase, which was in favor of the placebo ($P = 0.01$).

MFSQ

At the end of the run-in period after 3 cycles of COC use only, small and statistically significant decreases were found for the Global score (change from baseline to end of run-in period (cycle 3) -4.0 ±10.6; $P = 0.002$) and the domains Sexual interest (-1.7±4.5; $P = 0.0005$) and Orgasm (-1.5±3.0; $P = 0.0001$) (Figure 2).

During the treatment period, no statistically significant differences were found between the DHEA and the placebo group (Figure 2).

Q-LES-Q

In general, mean Q-LES-Q global scores were high throughout the study i.e. during COC use alone and during the treatment period (≥67%) and no statistical differences were found between DHEA and placebo.

Safety and tolerability

No clinically relevant changes were noted for vital signs, body weight and safety laboratory parameters (data not shown). All reported adverse events (AEs) were of mild or moderate intensity. During treatment with DHEA or placebo a total of 116 AEs were reported. There was no difference between the treatment groups (57 for DHEA and 59 for placebo). AEs that were of moderate severity included hypercholesterolemia (10 in both groups) and hypertriglyceridemia (2 in both groups), vulvovaginal mycotic infection (one in the DHEA group), liver function test abnormal, anxiety, depressed mood and hirsutism (none for DHEA and one case per AE for the placebo group).

Skin characteristics

At baseline 20 from 99 women included showed mostly mild acne according to the investigator and 28 according to self-assessment. For seborrhea these number were 10 and 35 and for hirsutism 5 and 27, respectively. During COC use only, there was an improvement of acne and seborrhea. Most women did not experience skin problems during the study and those who did, reported mild abnormalities in the majority of cases, with no reports of severe cases. Two women using DHEA and one using placebo reported acne as a mild AE. One woman treated with placebo reported hirsutism as a moderate AE. According to the investigator's judgment there were no statistically significant differences between the two treatment groups. According to the subject's assessment, women in the DHEA group reported

more cases of mild and moderate acne compared to women in the placebo group ($P < 0.001$). However, at the end of DHEA treatment compared to baseline before COC use no significant differences were found for all androgen related skin symptoms. Detailed results on acne are provided in Table 2.

Discussion

We have confirmed the suppression of androgen levels when using an EE/DRSP containing COC in a separate paper reporting the endocrine data from the present study [20]. Here we report the effect of this COC in healthy users without previous complaints regarding sexual function, mood or quality-of-life, as well as the effect of restoration of androgen levels by adding 50 mg DHEA to this COC, hypothesizing that such an intervention would have favorable clinical implications i.e. show improvements in sexual function, mood and/or quality of life compared to placebo (COC use alone).

In the first part of the study small, but highly significant, negative effects of a COC only were observed on sexual function in the MFSQ on the Global score and the domains Sexual interest and Orgasm. Positive significant effects were found on menstrual cycle related symptoms as measured by the MDQ, except for the domain Arousal, showing negative effects. According to the literature, the effect of COC use on these parameters is inconsistent [3, 21, 23-26, 39]. In some studies the EE/DRSP COC used has been shown to improve the MDQ domains Water retention and Negative affect [40-42], but this was not observed in our study. Several publications report positive effects of EE/DRSP COCs on mood and sexual function [40-45], whereas others report negative effects [1, 2].

In the second part of the study after 6 treatment cycles of the EE/DRSP COC, combined with either 50 mg DHEA or placebo, some small effects in favor of DHEA were

found on menstrual cycle related complaints in three phases of two domains of the MDQ: Autonomic reactions (menstrual and pre-menstrual phases), and Behavior change (inter-menstrual phase). Placebo was better in the domain Arousal. No effect of DHEA was observed in the MFSQ and the Q-LES-Q. The clinical relevance of the small changes observed are uncertain and may even be related to multiple testing.

The effect of COC use on mood and sexual function has been questioned [3, 21, 23-26, 39], although in a recent paper by a group of COC experts the concept of "Oral Contraceptive-Associated Sexual Dysfunction" has been presented [4]. The COC only data from our study support the view that COC use may have a negative effect on sexual function. Only a few studies report combined investigations of the effect of COCs on androgens and the occurrence of behavioral side effects and those studies also report conflicting results [1, 2, 5, 27, 46-51]. Potential reasons for these inconsistences include differences in subject characteristics such as age, BMI, genetic factors including individual sensitivities to androgen reduction, and differences in study design such as endpoints, type of oral contraception and duration of treatment [3, 5, 15, 27].

There may be several other explanations for the questionable clinical effects of DHEA in the present study. First, the study was powered to evaluate the effect of DHEA on the levels of total T and not to find statistical differences for the questionnaires used. Therefore, the group sizes may have been too small to reach statistical significance. This is supported by the observation of many trends in favor of DHEA in this study (Figures 1 and 2). Second, a potential inclusion bias is that those women who are sensitive to testosterone changes and have experienced such changes during earlier COC use, may not have volunteered to participate in this study. Third, the sensitivity of the questionnaires used may have been too low to find subtle behavioral differences in healthy young women without complaints. In another study we have used a sexual function diary, which appeared to be more sensitive, as

demonstrated in a study on sexual function in postmenopausal women [52]. Fourth, the endocrine effect of the 50 mg dose of DHEA may have been insufficient in combination with the EE/DRSP COC used, due to the strong increase of SHBG that binds T and interferes with an adequate increase of free T [20]. Full restoration of total T levels to baseline levels was achieved, but free T levels were only restored by 47%. For an optimal judgment of the clinical effects of normalizing T during COC use, it may be necessary to restore free T completely.

This raises the issue of the DHEA dose used. A daily dose of 50 mg DHEA was chosen, based on earlier dose-finding studies in elderly individuals with normal levels of SHBG and not using other drugs [29]. In addition, we have shown earlier that a dose of 50 mg DHEA could normalize free T levels in combination with a COC containing the progestin levonorgestrel (LNG) [53]. COCs containing LNG hardly increase SHBG [19] and therefore, the clinical effect of androgen restoration in users of an EE/LNG COC by adding 50 mg DHEA may be more pronounced. For those COCs that increase SHBG, a higher dose of DHEA may be required to normalize free T and demonstrate clinical effects. However, a higher DHEA dose will also increase the levels of ADG further, which may enhance androgenic effects on the skin.

In this study, the daily co-administration of 50 mg DHEA did not give rise to safety concerns, as supported by data from the literature [54-61]. As demonstrated also in this study COCs improve androgenic skin symptoms and an important question was whether DHEA use would have negative effects on androgen related skin symptoms. COCs act by reducing androgen levels and by blocking the androgen receptors [62-66]. COCs may also inhibit the activity of skin 5α -reductase, which results in a reduction of the conversion from T to DHT [65, 67, 68]. Despite a significant increase of ADG in the current study, the co-treatment with DHEA did not worsen skin symptoms, but it negated the beneficial effect of the COC on acne

partially according to the judgment of the investigator and completely according to the self-assessment of the subjects. Therefore it seems advisable not to use an androgen restored COC in women with androgen related skin characteristics.

In conclusion, the 50 mg dose of DHEA used in this study may have been too low for this particular COC, since levels of free T were only restored by 47% compared to baseline before COC use. A well-balanced judgment of the clinical consequences of the concept of normalizing androgens during COC use may require complete normalization of free T, lost for 86% due to COC use in this study.

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Table 1: Effect of 50 mg DHEA or placebo daily co-administration on menstrual cycle symptoms as measured by the Moos Menstrual Distress Questionnaire (MDQ), scores for the domains Pain, Autonomic reactions, Negative affect, Behavior change, and Arousal during different phases of the cycle, in women using a COC containing 30 µg ethinylestradiol and 3 mg drospirenone

		Menstrual phase			Pre-menstrual phase			Inter-menstrual phase		
Variable	**Treatment**	**Cycle 3**	**Cycle 9**	**Change from cycle 3 to cycle 9**	**Cycle 3**	**Cycle 9**	**Change from cycle 3 to cycle 9**	**Cycle 3**	**Cycle 9**	**Change from cycle 3 to cycle 9**
Pain	DHEA	45.0±12.6	42.8±10.6	-2.0±13.0	47.3±13.1	45.4±9.5	-2.1±12.4	50.0±15.1	49.2±10.5	-0.9±14.2
	Placebo	49.3±17.2	48.0±16.0	-1.1±14.7	48.9±16.0	48.8±14.0	-0.8±9.0	51.3±20.7	54.0±16.4	3.7±18.2
Autonomic reactions	DHEA	46.7±10.6	44.8±9.2	**-2.0±11.5***	48.2±13.2	45.0±5.0	**-3.1±11.1****	49.1±7.9	48.8±8.4	-0.5±10.5
	Placebo	50.6±15.1	50.7±14.8	0.7±11.6	49.2±12.1	51.3±16.6	2.9±17.2	54.9±18.8	51.3±13.4	-2.3±22.5
Negative affect	DHEA	45.7±15.8	42.1±14.0	-4.2±14.8	45.4±13.0	43.4±12.2	-2.8±12.9	48.3±11.1	46.5±14.3	-3.1±14.2
	Placebo	46.4±12.9	45.4±15.3	-0.8±15.2	45.3±12.0	45.9±13.4	0.8±13.6	47.6±15.3	50.2±16.4	2.1±20.5
Behavior change	DHEA	47.0±9.7	46.0±12.6	-1.7±12.2	48.8±12.0	49.0±14.8	-0.5±15.6	51.1±11.6	50.8±14.6	**-1.4±14.6***
	Placebo	54.6±16.9	51.7±19.5	-2.7±17.8	55.6±19.2	55.9±19.9	0.8±18.3	57.8±24.3	60.4±25.2	3.6±32.3
Arousal	DHEA	46.2±13.9	42.7±11.4	-3.4±10.2	47.3±14.6	42.1±10.2	**-5.0±9.3****	46.4±13.4	42.6±9.6	-3.7±10.9
	Placebo	45.6±12.0	43.9±11.3	-1.0±11.7	46.3±12.5	46.5±13.9	1.0±13.2	45.4±11.6	44.3±9.7	-0.6±9.8

Data are expressed as mean ± standard deviation; cycle 3 = the end of the run in period with COC alone; cycle 9 = end of treatment period; **bold***=$P < 0.05$ between the two treatment groups (DHEA vs placebo) at cycle 9 with regard the change from cycle 3 (COC use alone); **bold****=$P < 0.01$ between the two treatment groups (DHEA vs placebo) at cycle 9 with regard the change from cycle 3 (COC use alone); COC, combined oral contraception; DHEA, dehydroepiandrosterone; n, number

Table 2. Effect of 50 mg DHEA daily co-administration compared to placebo on skin characteristics in women using a COC containing 30 µg ethinylestradiol and 3 mg drospirenone

Variable	Treatment	Assessment		Baseline	End of run-in period (Cycle 3: COC only)	Treatment period (Cycle 6)	End of treatment period (Cycle 9)
Acne	DHEA	Investigator	n	49	49	49	49
			none	37	47	45	42
			mild	12	2	4	7
			moderate	0	0	0	0
			severe	0	0	0	0
		Subject	n	49	49	49	49
			none	32	40	37	34
			mild	15	9	9	13
			moderate	2	0	3	2
			severe	0	0	0	0
	Placebo	Investigator	n	50	50	48	48
			none	42	46	45	45
			mild	7	3	3	3
			moderate	1	1	0	0
			severe	0	0	0	0

Subject	n	50	50	48	48
	none	39	38	43	42
	mild	10	11	4	6
	moderate	1	1	1	0
	severe	0	0	0	0

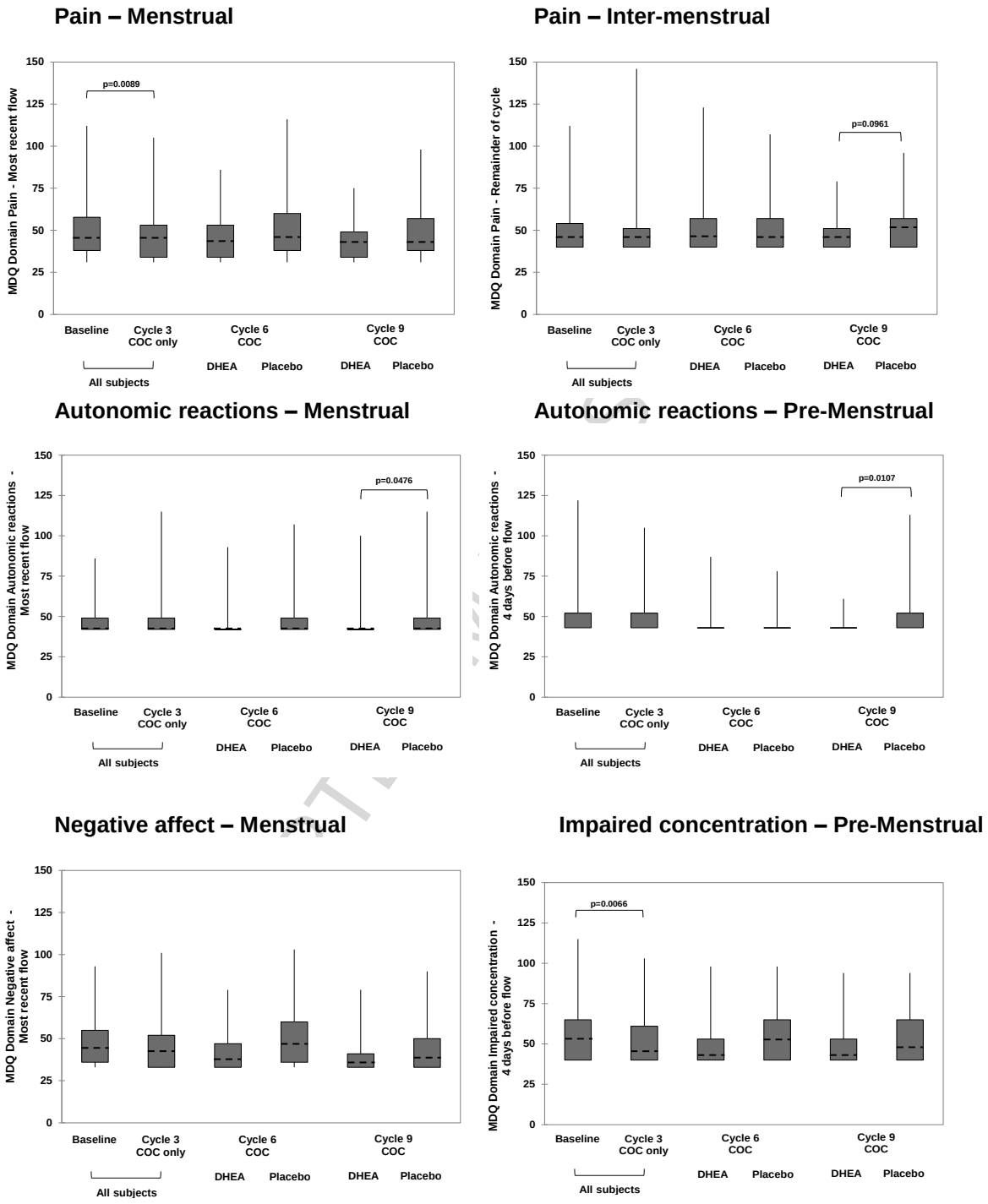

Figure 1. Effect of COC use alone and of 50 mg dehydroepiandrosterone (DHEA) daily co-administration on menstrual cycle symptoms as measured by the Moos Menstrual Distress Questionnaire (MDQ), scores for the domains Pain, Autonomic reactions, Negative affect and Impaired concentration during different phases of the cycle, in women using a COC containing 30 µg ethinylestradiol and 3 mg drospirenone. In these box plots, half of the data (percentile 25-75) is represented by the boxes. Dark dashed lines in the boxes indicate the median. T-bars from the boxes extend to the minimum and maximum; COC, combined oral contraceptive.

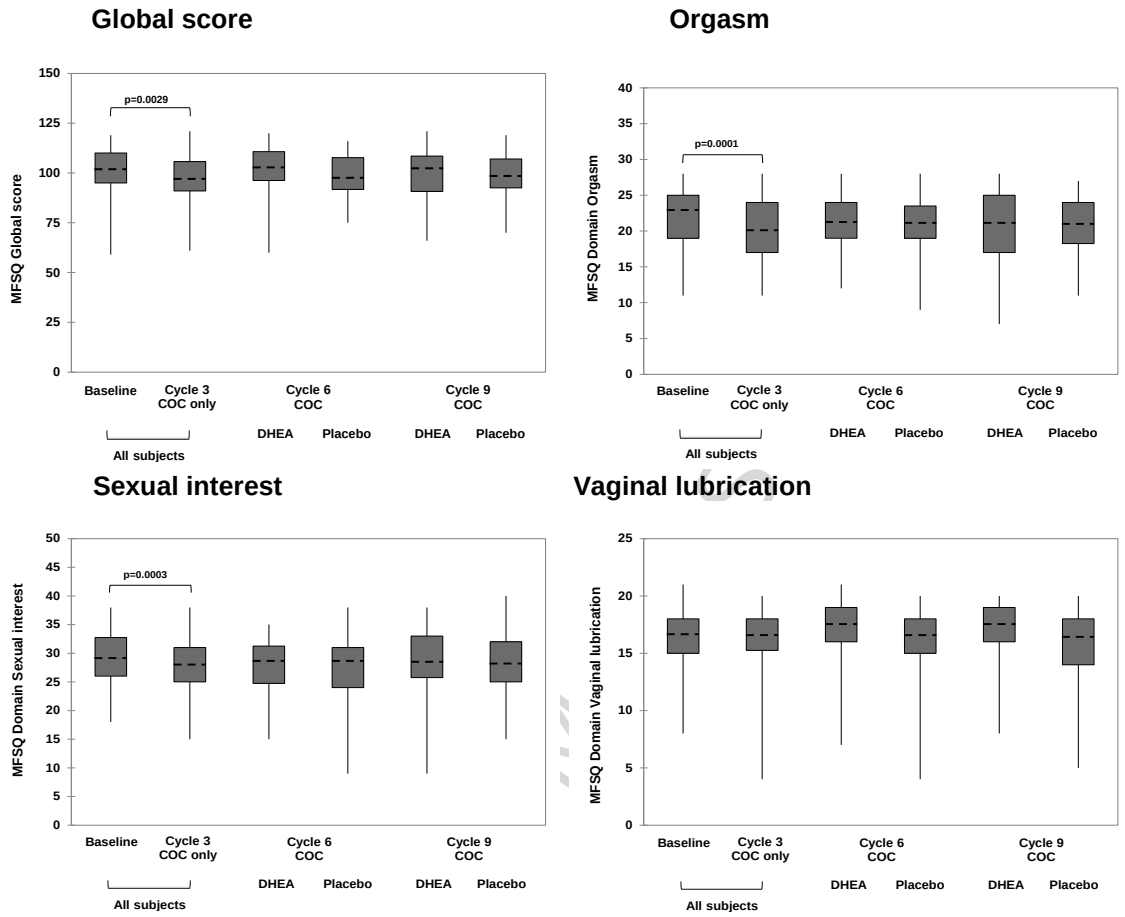

Figure 2. Effect of COC use alone and of 50 mg dehydroepiandrosterone (DHEA) daily co-administration on female sexual function as measured by the McCoy Female Sexuality Questionnaire (MFSQ) for the Global score and the domains Orgasm, Sexual interest and Vaginal lubrication in women using a COC containing 30 µg ethinylestradiol and 3 mg drospirenone. In these box plots, half of the data (percentile 25-75) is represented by the boxes. Dark dashed lines in the boxes indicate the median. T-bars from the boxes extend to the minimum and maximum; COC, combined oral contraceptive.