

IMPACT OF ORAL DHEA SUPPLEMENTATION ON ANDROGEN LEVELS IN WOMEN USING COMBINED ORAL CONTRACEPTIVES: A RANDOMIZED STUDY

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SUMMARY

Background: Combined oral contraceptives (COCs) reduce androgen levels, particularly Testosterone (T), by inhibiting ovarian and adrenal androgen synthesis and increasing Sex Hormone-Binding Globulin (SHBG). This can lead to testosterone deficiency, which is associated with negative effects on well-being, mood, energy, cognitive function, sexual functioning, muscle mass, and bone density.

Objective: To evaluate the effects of adding oral Dehydroepiandrosterone (DHEA) to Combined Oral Contraceptives (COCs) on the hormonal profile in Caucasian women.

Materials and Methods: A randomized, double-blind, placebo-controlled trial was conducted with 35 healthy Caucasian women aged 21-35 years (BMI: 18.5-25 kg/m²) who used a COC containing 30µg ethinyl estradiol (EE) and 150µg Levonorgestrel (LNG). Participants discontinued COC use for three menstrual cycles before being randomized to receive either COCs with 50 mg/day DHEA (n=18) or placebo (n=17) for six cycles. Hormonal levels were measured at baseline and after 1, 3, and 6 months of treatment.

Results: COC use significantly reduced Total Testosterone (by 56.2%), Free Testosterone (by 65.7%), Dehydroepiandrosterone, Dehydroepiandrosterone Sulfate, and Androstenedione levels while increasing SHBG concentration (P<0.001). Adding DHEA to COCs restored both Free and Total Testosterone levels to baseline (P<0.001).

Discussion: The addition of DHEA to COCs was effective in maintaining physiological androgen levels, potentially counteracting the adverse effects of COCs on female sexual function and overall well-being.

Conclusion: Adding 50 mg/day DHEA to EE/LNG-containing COCs maintains physiological levels of Free and Total Testosterone in Caucasian women, potentially mitigating the adverse effects of

COCs on female sexual function. Further comprehensive clinical trials are warranted to evaluate these clinical effects.

Keywords: combined oral contraceptives, testosterone, dehydroepiandrosterone, androgen deficiency, sex hormone-binding globulin, female sexual function.

INTRODUCTION

Combined oral contraceptives (COCs) are known to reduce the levels of androgens, especially Testosterone (T), by inhibiting ovarian and adrenal androgen synthesis and by increasing levels of Sex Hormone-Binding Globulin (SHBG).¹

As a result of the action of COCs, which involves the suppression of gonadotropins, they may have a direct inhibitory effect on the synthesis of ovarian and adrenal androgens and blood testosterone levels. Testosterone, the most potent circulating androgen in women, can decrease by up to 50% due to the action of COCs.^{1,2}

Three possible underlying mechanisms may be held responsible for this effect: (i) Suppression of ovarian androgen synthesis, (ii) increased SHBG concentrations, and (iii) suppression of adrenal androgen synthesis.¹

Testosterone deficiency is thought to be associated with a broad range of undesired effects, including diminished well-being and quality of life, mood changes (depression, irritation, moodiness), loss of energy, cognitive disturbances, interference with optimal sexual functioning⁸, declining muscle mass and strength and lowering of bone density.¹

A Significant reduction of androgen levels caused by Combined Oral Contraceptives (COCs) is a reliable mechanism by which COCs may adversely affect sexual function in a subset of women.^{1,8}

Maintaining physiological levels of androgens, especially Free Testosterone (FT), may ameliorate these adverse effects of COCs. This can potentially be achieved by adding dehydroepiandrosterone (DHEA) to Combined Oral Contraceptives (COCs).⁴⁻⁷

Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone Sulfate (DHEAs) are endogenous steroid hormone precursors, which are produced by the adrenal gland and the brain and through partial metabolism to testosterone, characterized by an androgenic nature.^{3,4,7}

Because the liver partially metabolizes oral DHEA into Testosterone³⁻⁵, it could, in principle, be incorporated as a prodrug into a COC pill, thereby maintaining T levels in women who use these COCs.³

Adding Dehydroepiandrosterone (DHEA) to COCs may maintain physiological levels of androgens and ameliorate adverse effects associated with androgen deficiency.³⁻⁷

OBJECTIVE

To evaluate the effects of adding oral Dehydroepiandrosterone (DHEA) to Combined Oral Contraceptives (COCs) on the hormonal profile in Caucasian women.

METHODS AND MATERIALS

We conducted a rigorous randomized, double-blind, placebo-controlled trial involving 35 healthy Caucasian women (age range: 21-35 years; body mass index (BMI) range: 18.5-25 kg/m²) who used a Combined Oral Contraceptive containing 30µg ethinyl estradiol (EE) with 150µg Levo-

norgestrel (LNG) for at least three months. Levonorgestrel was chosen because of its intrinsic androgenic effects (4).

Study participants discontinued OC use for at least three menstrual cycles, after which they were randomized by random selection to a study group to receive 30 µg EE/150 µg LNG containing COCs together with oral DHEA 50 mg/Daily dose (n=18) or placebo group (n=17) for the following six cycles.

The study protocol was approved by the local ethical committee of Tbilisi State Medical University, and informed consent was obtained from each participant before the study began.

The exclusion criteria included estrogen-dependent neoplasia—current or previous—endocrine conditions, thromboembolic disease, and liver, pancreatic, or renal diseases.

Before the study, we performed a gynecological examination, pelvic transvaginal ultrasound scan (TVUS) before and after 1, 3, and 6 months of treatment, and blood tests to evaluate coagulation parameters and mammography.

We determined serum levels of Free testosterone (FT), Total Testosterone (TT), Sex Hormone Binding Globulin (SHBG), Dehydroepiandrosterone (DHEA), Dehydroepiandrosterone Sulfate (DHEAs), Androstenedione (AD), Estradiol (E2), Estrone (E1) and Albumin during the screening period, at baseline and after 1, 3 and 6 months of treatment.

RESULTS

Taking Combined Oral Contraceptives reduced the levels of all determined androgens - for Total Testosterone by 56.2%, for Free Testosterone by 65.7% (P<0.001), and also reduced the levels of Dehydroepiandrosterone, Dehydroepiandrosterone Sulfate, and Androstenedione, while increasing the concentration of Sex Hormone Binding Globulin (P<0.001).

Adding DHEA to COCs significantly increased the levels of all measured androgens compared to placebo: both Free Testosterone (FT) and Total Testosterone (TT) levels were restored to their baseline levels (Fig 1 - A, B). (P<0.001).

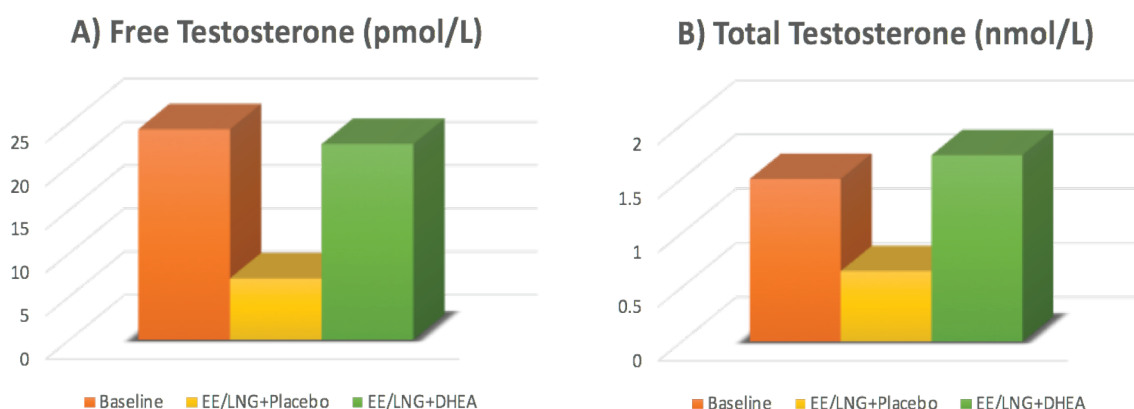


Figure 1.

Adding DHEA to Combined Oral Contraceptives did not affect Sex Hormone Binding Globulin (SHBG) levels (Fig 2). ($P < 0.001$)

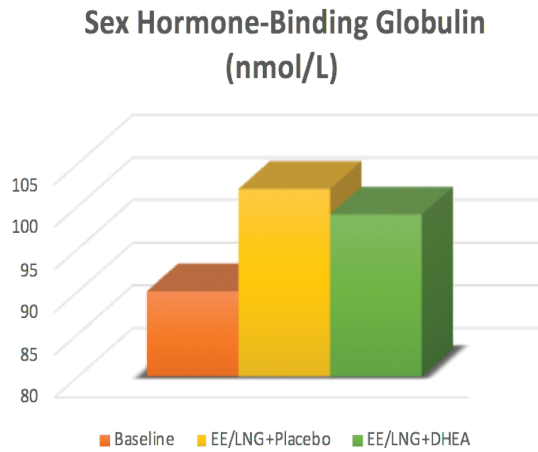


Figure 2.

Moreover, adding DHEA significantly increased the levels of Dehydroepiandrosterone (DHEA) and Dehydroepiandrosterone Sulfate (DHEAs) (Fig 3). ($P < 0.001$)

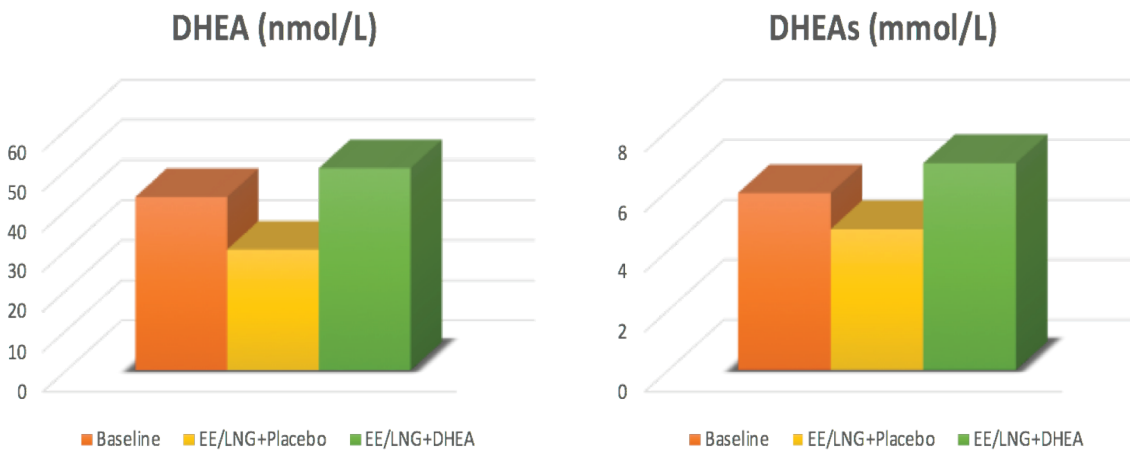


Figure 3.

Adding DHEA significantly increased the levels of Estrone (E1) and decreased the levels of Estradiol (E2) (Fig 4 - A, B). ($P < 0.001$)

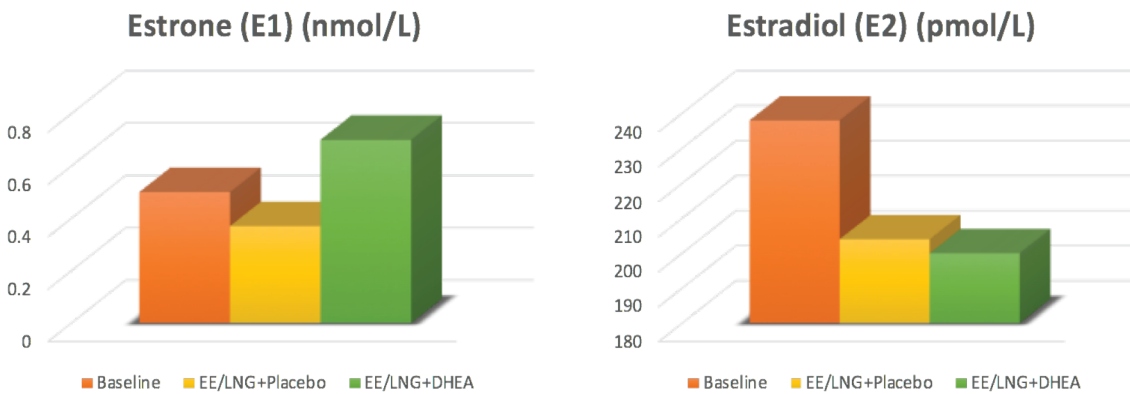


Figure 4: A

Figure 4: B

DISCUSSION

The use of combined oral contraceptives (COCs) is associated with decreased androgen levels and increased Sex Hormone Binding Globulin (SHBG) concentrations. Adding DHEA to Ethinyl Estradiol/Levonorgestrel-containing COC restored both Free and Total testosterone levels to their physiological values.

Conclusion

Based on the results of our study, we can conclude that the addition of 50 mg/daily dose of oral DHEA to an EE/LNG-containing COC maintains physiological levels of Free and Total Testosterone in Caucasian women and thus may potentially ameliorate the adverse effects of COCs on female sexual function.

The results of our study provide the basis for planning and conducting more extensive, comprehensive, and modeled clinical trials to evaluate clinical effects.

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