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# Effect of low-dose oral contraceptive on gonadotropins, androgens, and sex hormone binding globulin in nonhirsute women*,†

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The effectiveness of a low-dose oral contraceptive (OC) in suppressing plasma levels of gonadotropins, ovarian, and adrenal androgens and stimulating sex hormone-binding globulin (SHBG) was evaluated prospectively in nonhirsute women. Thirty-three women ingested 35 μg of ethinyl estradiol and 1 mg of norethindrone beginning within day 1 to 5 of the menstrual cycle. Baseline levels of luteinizing hormone, follicle-stimulating hormone, total testosterone (T), androstenedione (A), dehydroepiandrosterone sulfate (DHEAS), and SHBG were obtained before ingestion of the OC and repeated after 3, 6 and, 9 months of OC use on day 1 to 5 of the OC "cycle". A significant suppression of gonadotropin levels is seen in nonhirsute women. Sex hormone binding globulin is consistently stimulated by the low-dose OC. A significant suppression of T and DHEAS is observed. No change was seen in levels of A. The demonstrated effects become evident at 3 months and are maintained at 6 and 9 months. Fertil Steril 53:35, 1990

The use of combined oral contraceptives (OCs) is associated with many metabolic changes and side effects. OC associated changes such as increased risk of peripheral arterial phenomena, myocardial infarction in smokers, liver tumors, hypertension, and changes in glucose metabolism appear to be estrogen dependent.[1-5] To reduce the magnitude of these changes, the dose of estrogens has been markedly reduced such that most OCs in the United States contain 30 to 35 μg of ethinyl estradiol ($EE_2$). There has been a trend to decrease the content of progestogens as well. Progestins decrease high-density lipoprotein (HDL)-cholesterol and increase low-density lipoprotein (LDL)-cholesterol an effect that promotes heart disease. The arteriosclerotic process responsible for heart attacks and strokes is attributed to the progestin component. Oral contraceptive with high progestin content, unlike today's low-dose formulations, produce the unfavorable lipoprotein levels.[6]

Oral contraceptives containing 50 to 80 μg of $EE_2$ or it's equivalent have been commonly used to treat both idiopathic hirsutism and hirsutism associated with hyperandrogenemia. Traditionally, OCs have been used to suppress androgens of ovarian origin. However, several studies have indicated suppression of adrenal androgens such as dehydroepiandrosterone sulfate (DHEAS) with OC.[7,8] Given the

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combined decrease in the OC components, there is the possibility that suppression of pituitary-ovarian/adrenal function may not be as "effective" as with higher dose formulations. Additionally, little normative data is available on the long term effects of low dose OCs on these parameters. The present study was designed to evaluate the short and long term effect of a low-dose OC on ovarian and adrenal function in normal women.

## MATERIALS AND METHODS

### Subjects

Thirty-three healthy, normally menstruating, nonhirsute women aged 18 to 35 years were studied. None had received steroid treatment within the last 3 months before the study. The study protocol was approved by the internal review board and informed consent was obtained from each volunteer. An OC containing 35 μg of $EE_2$ and 1 mg of norethindrone (NET) was begun within day 1 to 5 of the menstrual cycle. Serum samples were obtained between 7 to 9 A.M. before beginning OCs and again at 3, 6, and, 9 months on day 1 to 5 of the OC "cycle". Day 1 of the OC cycle is the first day of OC ingestion. All sera were stored at −20°C until analysis. All patient sera were included in the same assay to eliminate interassay variability.

### Assay Methods

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were quantified by direct radioimmunoassay (RIA) using a second antibody precipitation method to separate bound and free reactants.[9,10] LER-907 standards were used for both LH and FSH. Sera were supplied by National Institutes of Health (Bethesda, MD). Iodinated antigens were purchased from New England Nuclear (Boston, MA). Second antibody was obtained from Pell Freeze Inc. (Rogers, AK). The FSH assay sensitivity is 25 μg/mL and 10 μg/mL for the LH assay. The intra-assay coefficient of variation was 2.1% for FSH and 3.2% for LH. Sex hormone-binding globulin (SHBG) values were determined by RIA using a commercial kit (Techland S.A., Liege, Belgium). The sensitivity of the assay is 10 μmol/L. Androstenedione (A), DHEAS, and total T were also determined by RIA according to the manufacturers recommendation (Diagnostic Products Corporation, Los Angeles, CA). The sensitivity of the A assay is 0.02 μg/mL, 2.1 μg/dL for DHEAS and 11 μg/dL for T. The intra-assay coefficient of variation was 3.7% for SHBG, 4.3% for A, 0.51% for DHEAS, and 1.5% for T.

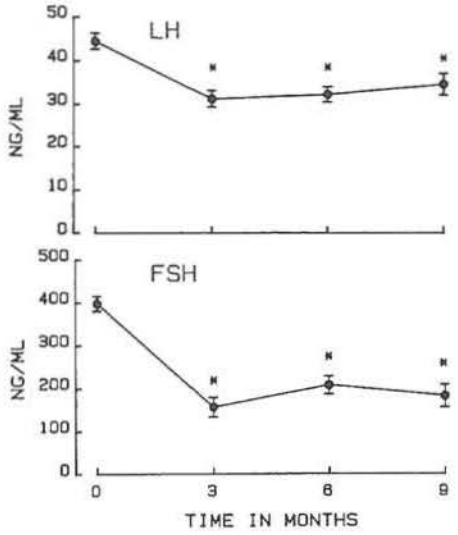


**Figure 1** Effects of a low-dose OC on mean (±SE) serum FSH and LH levels at baseline and 3, 6, 9 months. *Significant differences determined by Dunnett's multiple range test ($P < 0.005$).

### Statistical Methods

Repeated measures analysis of variance and covariance was used for analysis of data (Biomedical Data Program [BMDP] Statistical Software, Inc. Los Angeles, CA). Once statistical significance was established with analysis of variance, Dunnett's multiple range test was used to compare the baseline data with that obtained at 3, 6, and, 9 months separately (BMDP Statistical Software, Inc.). Results are expressed as mean ± standard error of the mean (SEM).

## RESULTS

The changes observed for gonadotropins are shown in Figure 1. Follicle-stimulating hormone levels were significantly reduced from baseline at 3 months, 6 months, and 9 months ($P < 0.002$). The maximum decrease in FSH occurred at 3 months (61%). Similarly, LH was maximally suppressed from baseline by 30% at 3 months with continued suppression at 6 and 9 months ($P < 0.0001$).

The mean sex hormone binding globulin level before treatment was 65.1 ± 4.7 mmol/L as seen in

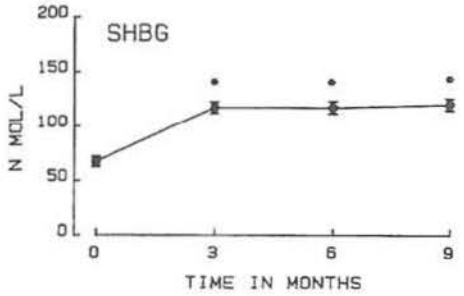


**Figure 2** Effects of a low-dose OC on mean (±SE) serum SHBG levels at baseline and 3, 6, 9 months. *Significant differences determined by Dunnett's multiple range test ($P < 0.001$).

Figure 2. A statistically significant increase occurred at 3 months, which continued at 6 months and 9 months ($P < 0.0001$).

Serum DHEAS was significantly reduced after 3 months and 6 months of low-dose OC ($P < 0.028$). At 9 months DHEAS remained suppressed, as seen in Figure 3.

The plasma levels of A at 3 months, 6 months, and 9 months were not significantly different from baseline. Total testosterone was significantly decreased at 3 months. The effect was maintained at 6 months and 9 months ($P < 0.0001$).

## DISCUSSION

Our results are the first to demonstrate that a "low dose" monophasic OC significantly suppresses serum immunoreactive gonadotropin levels in normally menstruating women when compared with baseline in the early follicular phase. A smaller study by Carr et al.[11] in four women using a "higher dose" OC (1.0 mg of NET and 80 μg of mestranol) found a suppression of serum LH to undetectable levels (<20 ng/mL) and a marked decrease of serum FSH that was independent of the time before the contraceptive induced withdrawal bleed. A study by Dericks-Tan et al.[12] using a combined low-dose preparation, while showing a trend toward decreased gonadotropins, failed to demonstrate a statistically significant difference. However, significance was not obtained possibly because of the small sample size (N = 6). While our study shows a significant suppression of immunoreactive levels of both gonadotropins on low-dose OC, FSH showed a two fold greater decrease than LH (60% versus 30%). Such a result may have been anticipated since Franchimont et al.[13] reported that higher doses of $EE_2$ and its derivatives (mestranol and 1-hydroxyethinyl estradiol 1.3, diacetate) depressed both LH and FSH, whereas lower doses of $EE_2$ (20 μg) primarily suppressed serum FSH in postmenopausal women. Moreover, the less pronounced decline in LH seen in our study may explain the failure of Elstein and associates[14] to detect changes in urinary LH secretion, except for suppression of the ovulatory peak, in women taking 50 μg of mestranol. Taken together with the previously published data,[11-13] our results are consistent with a dose dependent gonadotropin suppression in normal cycling women administered OCs.

Because our data followed individual patients prospectively, it was possible to discern that a significantly larger number of women failed to show suppression of immunoreactive LH (11 of 33) than failed to show suppression of FSH (3 of 33) ($P < 0.02$). All (three) subjects who showed no suppression of FSH also showed no suppression of LH. It is widely postulated that differential control of gonadotropin secretion is regulated by inhibin, activin, and other ovarian secretory products. While

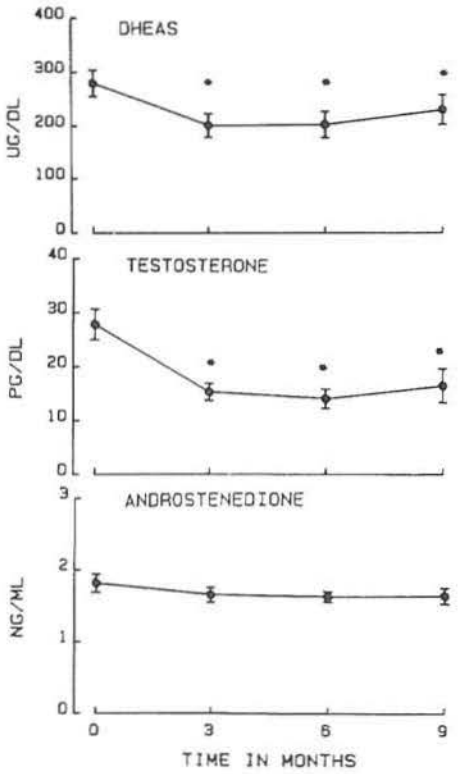


**Figure 3** Effects of a low-dose OC on mean (±SE) serum T, A, DHEAS levels at baseline and 3, 6, 9 months. *Significant differences determined by Dunnett's multiple range test ($P < 0.05$).

the effects of OCs on the secretion of these gonadotropin regulatory proteins is unknown, it is possible that relatively specific inhibitors of FSH are stimulated by either estrogens or progestins or that suppression of FSH stimulators occurs. Alternatively it could be argued that inability to detect equal changes in LH is an artifact that results from the greater pulsatile excursions in human serum of LH resulting from the much shorter half life of LH than FSH.

Sex hormone-binding globulin is substantially increased by estrogens and somewhat reduced by progestogens.[15,16] The effect of NET containing OC on SHBG is predominantly estrogenic rather than progestogenic. A levonorgestrel (LEV)-containing OC has been demonstrated to cause a decrease in SHBG capacity.[17] "Higher" dose OCs have been shown to increase SHBG in hirsute women.[18] Talbert and Sloan[19] have shown "low dose" NET-containing OCs significantly increase SHBG in women with polycystic ovarian disease. A short term study (20 days) of normal women demonstrated that low-dose $EE_2$ (30 $\mu$g) alone significantly increases SHBG.[20] Our data showing a significant rise in SHBG is consistent with this earlier work, and demonstrates for the first time that, in normal women on monophasic preparations, these alterations persist throughout the course of therapy when followed for as long as 9 months.

Dehydroepiandrosterone sulfate has been shown to be an important marker for adrenal androgen secretion in women.[21] The administration of estrogen alone results in either no change or an increase in DHEAS levels.[22,23] Klove[7] studied the effect of low-dose OCs on serum concentration of DHEAS in six nonhirsute women and noted that OCs containing NET but not LEV have a suppressive effect on adrenal androgen secretion. Our study confirms this finding with an NET-containing low-dose OC. A significant decline in DHEAS levels is seen and maintained for at least 9 months. The mechanism for this suppression is not established, although it has been suggested that plasma adrenocorticotropic hormone (ACTH) levels are decreased by OCs.[11]

Jung-Hoffman and Kuhl[24] noted a significant suppression of nonprotein bound T during treatment with both a low-dose monophasic OC and a triphasil preparation in normal women. Low dose OCs have been shown to suppress T in hirsute women with chronic anovulation.[8,18,24] Our study is the first long term study in normal women showing a significant suppression of protein bound T with a low-dose monophasic OC that is maintained to 9 months. Taken with the significant decrease in SHBG, the suppression would appear to be clinically significant.

Wild et al.[25] studied 15 hirsute women before and after the completion of one cycle of an OC containing 2 mg of NET and 100 $\mu$g of mestranol. Androstenedione was reduced by 47%. A reduction in the magnitude of the diurnal change in A synchronous with cortisol as well as a reduction in the A response to ACTH was seen. As noted previously, adrenal suppression seems to be dependent on the type of progestin. The low-dose OC used in this study contains half the progestin content that was used by Wild et al.[25] Our data in normal women show no change in A. Taken together with the previously published data[25] on hirsute women, we suggest there may be a dose dependent suppression of A which fails to reach significance at the low dose used in our study. The differing results may be explained by the different doses and populations (hirsute versus normal).

In conclusion, our data document that a low-dose OC containing 35 $\mu$g of $EE_2$ and 1 mg of NET reduces gonadotropin levels in nonhirsute, normally cycling women when compared with the early follicular phase. A differential effect is seen with FSH being more consistently suppressed than LH. Sex hormone-binding globulin is consistently stimulated by the low-dose OC. Our results show a significant decline in DHEAS levels that is sustained to 9 months. Serum total T is suppressed, but androstenedione did not significantly vary from baseline obtained in the early follicular phase. This large, prospective, longitudinal study provides important normative data for a commonly used monophasic low-dose oral contraceptive.

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