

## Early postoperative changes in testosterone, dehydroepiandrosterone sulfate, and sex hormone-binding globulin after hysterectomy with or without concomitant oophorectomy

Hikmet Hassa, M.D., Hüseyin Mete Tanir, M.D., and Nazan Ardic, M.D.

Eskisehir Osmangazi University School of Medicine, Department of Obstetrics and Gynecology, Meselik Kampusu, Eskisehir, Turkey

**Objective:** To investigate the cross-sectional associations of hysterectomy and oophorectomy status, chronological age, and body mass index with early postoperative plasma levels of total and free T, DHEAS, and sex hormone-binding globulin (SHBG).

**Design:** A cross-sectional study.

**Setting:** University hospital.

**Patient(s):** Ninety-two women age 35–47 years who were scheduled for hysterectomy and/or oophorectomy, advocated for benign gynecological pathologies.

**Intervention(s):** Ninety-two eligible premenopausal women underwent hysterectomy and/or oophorectomy, with plasma T, DHEAS, and SHBG levels assayed before surgery and during the postoperative period.

**Main Outcome Measure(s):** Effects of time  $\times$  operation and age  $\times$  operation interactions between oophorectomized and nonoophorectomized groups and within-subject main effect of time on plasma androgen levels.

**Result(s):** Of 92 women, hysterectomy alone was performed in only 49 (53.3%) cases. Oophorectomy, either unilateral or bilateral, was performed in 35.8% of cases. Age  $\times$  within-group interactions exhibited an important difference ( $P=.03$ ) in total T levels. The time  $\times$  between- and within-group interaction effects on plasma DHEAS levels of postoperative day 7, compared with day 1, were statistically significant ( $P<.001$ ). The effect of time  $\times$  group interaction was remarkable, in terms of SHBG levels during the postoperative period. Age  $\times$  oophorectomy interaction exhibited a statistically significant change of decline in DHEAS levels on postoperative day 7 ( $P=.05$ ).

**Conclusion(s):** The present study demonstrated a time and operation effect decline in plasma DHEAS levels. In contrast, the time  $\times$  operation interaction on SHBG levels exhibited an increase toward postoperative day 7. (Fertil Steril® 2006;86:981–9. ©2006 by American Society for Reproductive Medicine.)

**Key Words:** Hysterectomy, oophorectomy, testosterone, sex hormone-binding globulin, DHEAS

Hysterectomy is a commonly performed gynecologic operation. Bilateral oophorectomy is nearly always an elective procedure performed concurrently with hysterectomy and is indeed considered a prophylactic measure for ovarian cancer among certain high-risk women (1). Pathological processes and iatrogenic interventions that affect adrenal and/or ovarian function may reduce circulating androgen levels, compared with those of young healthy women (2). Overall, the absolute decline in both circulating T and adrenal DHEAS production becomes apparent in the decade preceding menopause (3, 4).

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Reprint requests: H. Mete Tanir, M.D., Eskisehir Osmangazi University School of Medicine, Department of Obstetrics and Gynecology, Meselik Kampusu, 26480, Eskisehir, Turkey (FAX: +90 222 2398412; E-mail: mtanir@superonline.com).

An overwhelming majority of studies suggest that T is the major androgen secreted by the postmenopausal ovary (5, 6). On the basis of other studies, there remains no compelling evidence that a decrease exists in the peripheral levels of T following oophorectomy (7, 8). A gradual decline in DHEAS has been proposed as the result of attenuated adrenal 17–20 desmolase activity in later life, and not related to gonadal function in the adult. Conversely, women who have undergone oophorectomy have one-half of the circulating levels of intact age-matched women, suggesting a role for ovarian communication with adrenals (9, 10).

The present study was conducted in an attempt to elucidate the cross-sectional influence of hysterectomy with and without oophorectomy, chronological age, and body mass index (BMI) on plasma levels of total and free T, DHEAS, and SHBG on postoperative days 1 and 7.

## MATERIALS AND METHODS

The present study was undertaken at a university hospital over a 3-year period, from January 2000 to January 2003. It included a total of 92 women, age 35–54 years, undergoing hysterectomy with or without adnexal removal at the Department of Obstetrics and Gynecology, Osmangazi University Hospital, Eskisehir, Turkey. Following the approval of the institutional review board, the informed consent of each participant was obtained. The main indications for hysterectomy were leiomyomas, chronic pelvic pain, and benign adenomatous hyperplasia of the endometrium. Eligibility criteria included: [1] intact uterus and ovaries, [2]  $\geq 1$  menstrual period in the previous 3 months, [3] no use of hormonal medication affecting ovarian function for  $\geq 6$  months before the study, [4] absence of endocrinopathies such as diabetes mellitus, thyroid, and adrenal disorders, [5] status of nonsmoker, and [6] absence of treatment with lipid- or glucose-lowering agents. The BMI ( $\text{kg}/\text{m}^2$ ) was used as an estimate of obesity. Cases were categorized as oophorectomized and nonoophorectomized on the basis of the type of operation. Concomitant unilateral salpingo-oophorectomy cases were included in nonoophorectomized group.

### Hormonal Assays

Plasma levels of T, free T, SHBG, and DHEAS were measured before surgery and on days 1 and 7 after surgery. Blood samples for hormone assay were obtained at 7:00–9:00 AM after a requested 12-hour fast. Plasma was separated and frozen at  $-70^\circ\text{C}$ .

The SHBG was measured by automated enzyme immunoassay using the Immulite system purchased in kit form from Diagnostic Products Corporation (Los Angeles, CA). Free T was determined by specific direct radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX). The DHEAS ( $\mu\text{g}/\text{dL}$ , conversion factor:  $\mu\text{g}/\text{dL} \times 0.02714 \mu\text{mol}/\text{L}$ ) and total T ( $\text{ng}/\text{dL}$ , conversion factor:  $\text{ng}/\text{dL} \times 0.00347 = \text{nmol}/\text{L}$ ) levels were measured using electrochemiluminescence immunoassay (Roche-Mannheim, Mannheim, Germany). Corresponding intraassay and interassay coefficients of variation were 7.7% and 13% for SHBG; 6.2% and 9.7% for free T; 2.1% and 2.5% for T; and 2.6% and 2.7% for DHEAS.

All participants in this study had no financial conflict of interest that existed between any commercial entity's products that are described, evaluated, or compared in this article.

### Statistical Analysis

The results were reported as means  $\pm$  standard error of the mean (SEM) because whole data were not representative of a total population. Repeated measures analysis of variance (ANOVA) was used to determine the change in primary endpoints over time. The time points of interest (the repeated measures factor) were defined as follows: [1] preoperative, 1 day before surgery; [2] postoperative 1, 1 day after surgery;

[3] postoperative 7, 7 days after surgery. The main parameters of interest were circulating levels of T, free T, SHBG, and DHEAS at the preceding time points. The ANOVA included a main effect for time, a main effect for operation type, and a time  $\times$  operation type interaction. The main effect of time was used to test whether the endpoint changed between the baseline and postoperative values in the sample as a whole. The time  $\times$  operation interaction tested whether mean changes differed between the oophorectomized and nonoophorectomized group.

To control confounding factors, such as age, time, and BMI, we added these variables as continuous covariates in ANOVA model. The Huynh-Feldt  $\epsilon$  value was used to compensate for the absence of sphericity by adjusting the associated degrees of freedom.

The Shapiro-Wilks test was applied to test the normal distribution of the data. A log transformation was applied to all hormone variables and to BMI to overcome the skewness of data. Paired *t* tests were performed to compare changes at follow-up from baseline on all outcome measures, despite the fact that data were not presented. Differences (%) of postoperative hormone levels from preoperative levels were calculated for each individual case. Comparisons of differences (%) of hormone levels, chronological age, and BMI between women in the oophorectomized and nonoophorectomized groups were performed with the use of the Mann-Whitney *U* test and Student's *t*-test where appropriate. The Pearson's correlation analysis ( $r_p$ ) was performed for the analysis of continuous variables.

Original values were used in the tables and box plots. Box plots display the median value (dark line in the interior of the boxes), with the 25th and 75th percentiles indicated by the lower and upper boundaries of the box, respectively. The whiskers extend to the largest and smallest observed values within 1.5 box lengths, and outlying values are indicated by circles or, if more extreme, by asterisks. Statistical analysis was performed using SPSS Statistical Software for Windows, version 12 (SPSS Inc., Chicago, IL) on a Pentium-based computer. A value of  $P < .05$  was considered statistically significant.

## RESULTS

The mean age did differ significantly between the nonoophorectomized ( $46.2 \pm 3.0$  years) and the oophorectomized group ( $41.7 \pm 3.5$  years,  $P < .001$ ). Furthermore, the BMI of the oophorectomized group was high ( $28.2 \pm 4.5 \text{ kg}/\text{m}^2$ ) compared with the nonoophorectomized group ( $26.3 \pm 3.7 \text{ kg}/\text{m}^2$ ,  $P < .05$ ). Ninety-six percent of all hysterectomies were performed via abdominal route. Oophorectomy was present in 35.8% ( $n = 35$ ) of all cases. Surgical indications were myoma uteri (80.4%), chronic pelvic pain (12.0%), and benign adenomatous hyperplasia (7.6%).

Participants were divided into three age groups:  $< 40$  years ( $n = 15$ ), 40–45 years ( $n = 26$ ), and  $> 45$  years ( $n = 51$ ). None

TABLE 1

## Operation-stratified distribution of hormones, age, and BMI.

	Nonophorectomized	Oophorectomized	P value
DHEAS ( $\mu\text{g/dl}$ ) <sup>a</sup>	122.7 $\pm$ 10.6 (27.7–291.0)	114.4 $\pm$ 9.0 (30.0–318.0)	>.05
T (ng/dL)	54.0 $\pm$ 5.7 (19.8–198.0)	49.5 $\pm$ 4.2 (7.4–160.0)	>.05
Free T (pg/mL)	1.4 $\pm$ 0.1 (0.4–4.4)	1.4 $\pm$ 0.1 (0.2–3.5)	>.05
SHBG (nmol/L)	50.4 $\pm$ 3.7 (15.4–155.0)	49.6 $\pm$ 2.8 (10.2–109.0)	>.05
Age (y)	41.7 $\pm$ 0.5 (35.0–49.0)	47.2 $\pm$ 0.4 (42.0–54.0)	<.001
BMI (kg/m <sup>2</sup> )	26.3 $\pm$ 0.6 (16.9–37.5)	28.1 $\pm$ 0.6 (18.1–44.9)	<.05

Note: All values are mean  $\pm$  SEM (minimum-maximum). SHBG = sex hormone-binding globulin; BMI = body mass index.

<sup>a</sup> Hormone values are not transformed by natural logarithm.

Hassa. Surgical menopause and hypoandrogenic state. Fertil Steril 2006.

of the women under the age of 40 had undergone oophorectomy, whereas removal of the ovaries was a part of the surgical procedure in 73.1% of the 40–45 years group and 17.6% of women >45 years, respectively. All oophorectomies were performed due to benign ovarian cysts and uncontrolled bleeding during periovarian tissue dissections of dense adhesions.

Operation type-stratified preoperative hormone distributions are listed in Table 1. Controlling age as a confounder, preoperative hormone levels did not significantly differ between women in the oophorectomized and nonoophorectomized groups ( $P>.05$ ). Operation type- and time-stratified distributions of hormones are listed in Table 2. Postoperative day 7 levels of DHEAS in the oophorectomized group were lower compared with nonoophorectomized group ( $P=.03$ ). Another striking finding was the fact that the SHBG level was remarkably higher in the oophorectomized group (58.9 nmol/L) compared with the nonoophorectomized group (50.1  $\pm$  3.9 nmol/L).

Figure 1 depicts the preoperative and postoperative day 1 and 7 hormone levels among the three age groups (<40, 40–45, and >45 years) in both the oophorectomized and nonoophorectomized groups. When age as a confounding factor was controlled, the effect of time interaction on total T levels remained statistically significant ( $F = 59.3$ ,  $P<.001$ ), despite no relevant association in between-group  $\times$  time interactions ( $F = 0.3$ ,  $P>.05$ ), as depicted in Figure 1. However, the within-group main effect of time revealed a significant decline of plasma T on postoperative day 7 compared with postoperative day 1 levels ( $F = 36$ ,  $P=.002$ ). No significant changes in total T levels were observed among the nonoophorectomized and oophorectomized groups, as presented in Table 1. The time effect ( $F = 0.2$ ,  $P>.05$ ), time  $\times$  group interaction ( $F = 0.4$ ,  $P>.05$ ), and time  $\times$  age  $\times$  group interactions ( $F = 0.2$ ,  $P>.05$ ) remained statistically nonsignificant, as depicted in Figure 1. Percent differences of total T values during postoperative follow-ups are also presented in Figure 2. As depicted in Figure 2, no statistically significant percentage changes were present among the two groups, on either postoperative day 1 or 7. As

illustrated in Figure 3, considering age as a covariable, time  $\times$  within- and between-group interactions indicated an important difference ( $F = 3.3$ ,  $P=.03$ ) in total T levels.

In terms of free T level changes, time  $\times$  age  $\times$  between-group interactions ( $F = 0.2$ ,  $P=0.44$ ) and time  $\times$  group ( $F = 0.1$ ) and time ( $F = 0.5$ ) interactions were not found to be significant, as depicted in Figure 1. Percentage changes from preoperative hormone levels on postoperative days 1 and 7 did not differ among the two groups, as illustrated in Figure 2. Similar to the total T level changes, there was a statistically significant within-subject main effect of time ( $F = 3.7$ ,  $P=.04$ ), as illustrated in Figure 3. No statistically relevant correlation existed between free T and SHBG levels on postoperative days 1 and 7 ( $r_p = 0.12$ ,  $P=.35$ ), irrespective of oophorectomy status. Oophorectomy did affect free T level changes but not those of SHBG, as illustrated in Figure 3.

As illustrated in Figure 1, in all three age groups, the within-group effects of time interactions remained significant ( $F = 0.5$ ,  $P=.05$ ). Given age as a covariable, further analysis demonstrated that time ( $F = 0.4$ ,  $P=.42$ ), time  $\times$  group interactions ( $F = 0.1$ ,  $P=.53$ ), and time  $\times$  group  $\times$  age interactions ( $F = 0.5$ ,  $P=.36$ ) were statistically nonsignificant. Percentage changes on postoperative day 7 were remarkably higher, compared with those on postoperative day 1, as demonstrated in Figure 2.

Time  $\times$  between-group ( $F = 48.1$ ,  $P<.001$ ) and time interaction ( $F = 5.9$ ,  $P<.01$ ) effects on plasma DHEAS levels remained statistically significant, as illustrated by Figure 3. In other words, hysterectomy with or without oophorectomy had a declining trend for DHEAS levels during the early postoperative course.

Time effects remained insignificant regarding the changes in SHBG levels ( $F = 2.6$ ,  $P>.05$ ), but time  $\times$  group interactions were statistically relevant ( $F = 3.8$ ,  $P=.02$ ). Taking Table 2 and Figure 1 into consideration, time, time  $\times$  group, and time  $\times$  group  $\times$  age interactions were nonsignificant if age was considered as a covariate. As depicted in Figure 2 and Figure 3,

**TABLE 2**

**Operation- and time-stratified distribution of hormones.**

	Preoperative			Postoperative day 1			Postoperative day 7		
	Non-O	O	P value	Non-O	O	P value	Non-O	O	P value
DHEAS ( $\mu\text{g/dl}$ ) <sup>a</sup>	122.7 $\pm$ 10.6	114.4 $\pm$ 9.0	> .05	112.0 $\pm$ 8.4	123.0 $\pm$ 10.4	> .05	91.9 $\pm$ 7.6	69.0 $\pm$ 5.4	< .05*
T (ng/dL)	54.0 $\pm$ 5.7	49.5 $\pm$ 4.2	> .05	41.0 $\pm$ 3.2	42.5 $\pm$ 4.0	> .05	31.8 $\pm$ 3.1	27.5 $\pm$ 2.3	> .05
Free T (pg/mL)	1.4 $\pm$ 0.1	1.4 $\pm$ 0.1	> .05	1.1 $\pm$ 0.1	1.2 $\pm$ 0.1	> .05	1.4 $\pm$ 0.2	1.2 $\pm$ 0.1	> .05
SHBG (nmol/L)	50.4 $\pm$ 3.7	49.6 $\pm$ 2.8	> .05	51.7 $\pm$ 4.1	48.2 $\pm$ 4.1	> .05	50.1 $\pm$ 3.9	58.9 $\pm$ 3.6	< .05*

Note: All values are mean  $\pm$  standard error of the mean (SEM). Non-O = nonoophorectomized; O = oophorectomized; SHBG = sex hormone-binding globulin.  
<sup>a</sup> Hormone values are not transformed by natural logarithm.

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in the oophorectomized group, plasma SHBG levels tended to increase. Percentage changes were also statistically significant between values of postoperative days 7 and 1 ( $P < .01$ ).

Obesity is one of the confounding factors that absolutely affects SHBG. However, all the results presented so far were uncontrolled for BMI. Taking BMI as a covariable into the model, although not presented in a separate figure, time ( $F = 2.0, P = .56$ ), time  $\times$  group ( $F = 1.8, P = .34$ ), and time  $\times$  BMI interactions ( $F = 1.9, P = .76$ ) did not reach statistical significance. No significant correlations were present between plasma levels of T, DHEAS, and free T changes and BMI.

**DISCUSSION**

This study reported a cross-sectional influence of hysterectomy with or without oophorectomy on endogenous hormone levels in premenopausal and perimenopausal women. Important findings of this study can be summarized as: [1] decreasing hormone levels over time, irrespective of the operation type, [2] a remarkable decline in DHEAS levels in the oophorectomized group, [3] a close interaction of chronological age with hormone level changes, and finally [4] an increase in SHBG levels in the oophorectomized group.

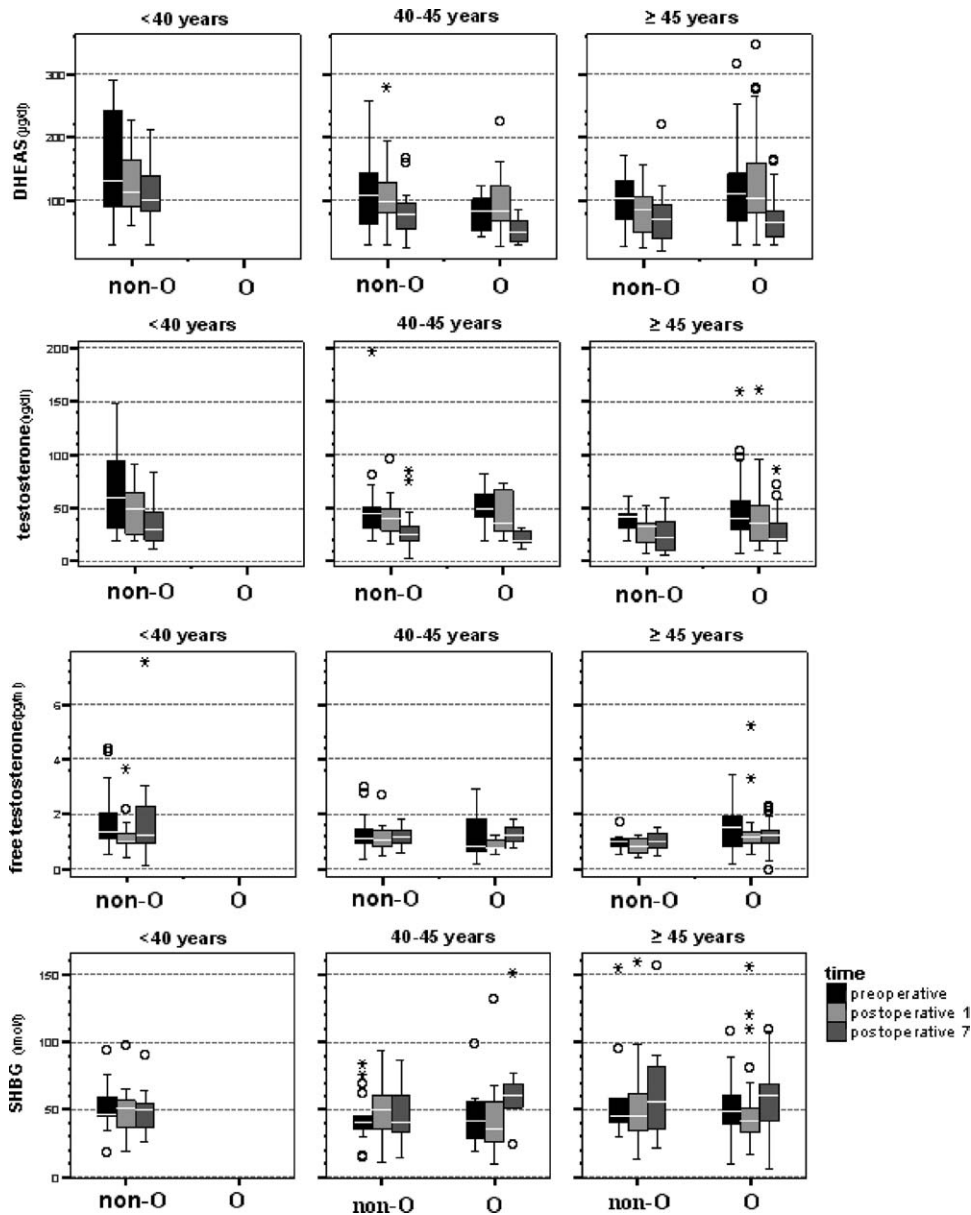
Hysterectomy is a commonly performed gynecologic operation. Under such circumstances, ovarian function may be adversely affected, most probably due to reduced arterial blood flow to the ovaries (11, 12). Our results were in accordance with previous studies indicating the fact that, even in the nonoophorectomized group, plasma T levels decreased. Riedel et al. (13) claimed that the extent of interference with the ovarian metabolism caused by hysterectomy is largely dependent on the blood supply type in the fraction of women reacting with ovarian failure and may vary with each investigated case. During data processing, we also observed such individual deviations of hormone levels.

Several lines of evidence had conflicting results regarding the effect of the menopausal transition on circulating androgen levels (3, 14, 15). In the study of Laughlin et al. (14), plasma T levels were 40% lower in women with oophorectomies than in intact postmenopausal women. Longcope et al. (3) failed to demonstrate any change in T over 80 months after the final menstrual period (FMP), whereas Rannevik et al. (15) documented a small but significant decline (-15%) in T and androgen levels within the 6-month period encompassing the FMP.

A major limitation of the present study is that the postoperative hormone levels were measured on day 7, which is much too soon to assume that these findings are permanent. Nevertheless, our analysis revealed that not only in the oophorectomized group, but also in the nonoophorectomized group, there was a decline in total T levels after surgery. Eventually, chronological age was found to have an influencing role on this decline together with operation effect per se, as depicted in Figure 1.

## FIGURE 1

Hormone levels before surgery (preoperative) and on postoperative days 1 and 7 among three age groups (<40, 40–45, and ≥45 years) in both oophorectomized (O) and nonoophorectomized (non-O) groups. Box plots display the median value (dark line in the interior of the boxes), with the 25th and 75th percentiles indicated by the lower and upper boundaries of the box, respectively. The whiskers extend to the largest and smallest observed values within 1.5 box lengths, and outlying values are indicated by asterisks. Time parameters are depicted in different colors. The Y-axis delineates the original hormone levels.



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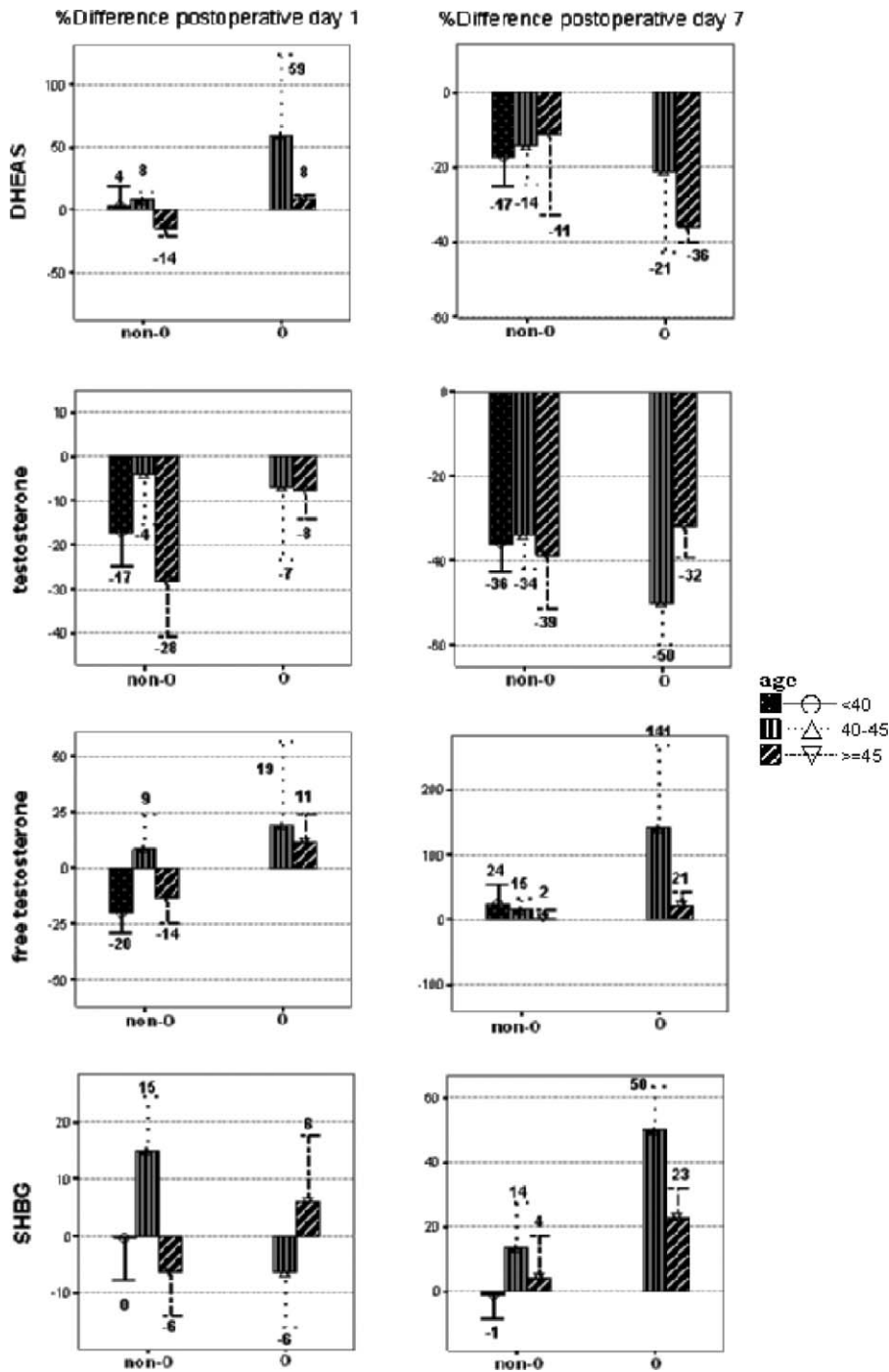
Despite age-related changes in DHEA and DHEAS, plasma cortisol levels vary little with age, implying the existence of a selective control mechanism above and beyond ACTH (16). Several studies have addressed the issue of gonadal–adrenal interaction with contradictory results, suggesting that gonadal dysfunction does not alter adrenal function (7, 17, 18). Meanwhile, Lasley et al. (18) argued that a

consistent change in ovarian function is related to circulating adrenal steroid levels in some middle-aged women, offering a logical explanation that supports the premise of a gonadal–adrenal interaction.

The result of present study also emphasized the fact that in both non- and oophorectomized women, a de-

**FIGURE 2**

Percentage changes in postoperative day 1 and 7 hormone levels compared with preoperative values among oophorectomized (O) and nonoophorectomized (non-O) groups. Values are mean  $\pm$  SEM. Percentage changes (\*) of each hormone are marked on the Y-axis.



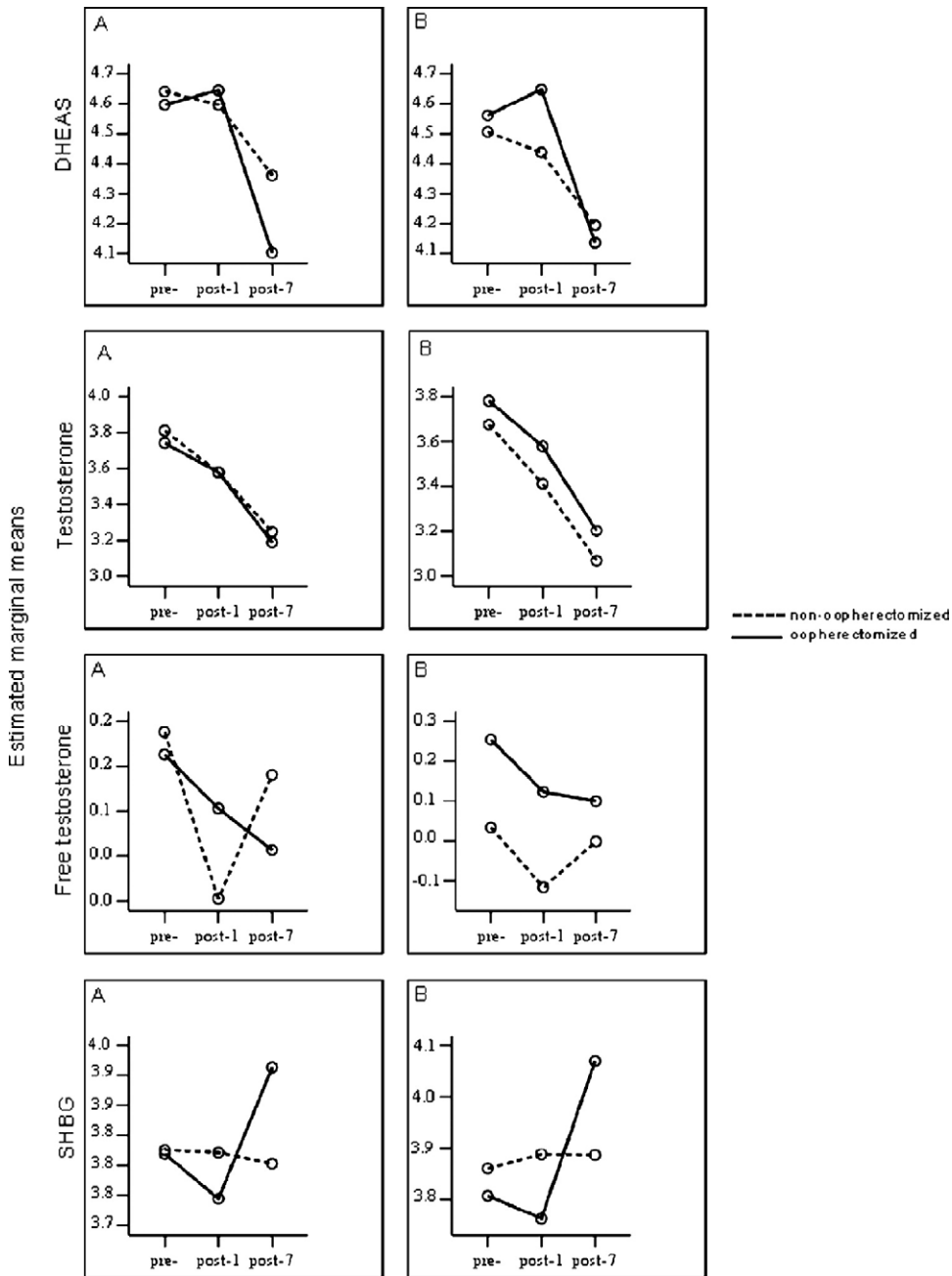
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crease in DHEAS levels were observed, more remarkably in the oophorectomized group. Understandably, this previously mentioned observation may appear to be in accordance with the gonadal-adrenal interaction hypoth-

esis. Several studies postulated that the ovary is not the androgen-producing organ, pointing out the lack of gonadotropin receptors and steroidogenic enzymes in the postmenopausal women (8, 19, 20). Unfortunately,

### FIGURE 3

Estimated marginal mean values of DHEAS, T, free T, and SHBG presented as time × group interactions without (A) and with age taken as a covariable (B). All values were transformed into logarithmic data. The X-axis indicates the time interaction at the preoperative (pre-), postoperative day 1 (post-1), and postoperative day 7 (post-7) time points.



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ovarian steroidogenesis was not evaluated entirely in the present study. Furthermore, some studies indicated that higher estrogen (E) levels from the premenopausal ovary may reduce adrenal androgen concentration (21, 22).

Within this context, several plausible and competing hypotheses have been proposed. The hypotheses are that E, through dopaminergic neurons in the brain, actually decreases bioavailable ACTH production, or may inhibit prolactin bioactivity, or act via some inhibitory molecule known

as cortical adrenal-stimulating hormone (22). At the present time, another controversial issue is whether the postmenopausal ovary is a major source for androgens.

In contrast, the presence of E receptors in the adrenal cortex of several animal species, including primates, suggests that E<sub>2</sub> is, most probably, a physiologically important regulator of adrenal steroidogenesis, and several investigators have suggested that menopause-associated E deficiency may further suppress adrenal androgens (23, 24). Almost all our surgical indications were attributed to myoma uteri or hyperplasia of the endometrium, which are associated with hyperestrogenic milieu. Moreover, we did not correlate the androgen hormone levels with E levels (preoperatively and postoperatively) and neither did we measure the intraovarian steroidogenesis that reflects a direct ovarian contribution. Obviously, these limitations hampered a robust interpretation of the data.

On the basis of the present study, it is worth noting that SHBG levels were influenced by ovarian status. As clearly illustrated in Figure 3, SHBG levels increased only in the oophorectomized group. Obviously, SHBG is an indirect measure of the T-E ratio and has been used as a marker for androgen status. In fact, the question of whether sex steroids can regulate SHBG, even in physiologic conditions, is still under debate, because physiologic changes in sex steroid levels do not always correlate with changes in SHBG. On the basis of our results, SHBG was negatively correlated with BMI, waist-to-hip ratio, and insulin and T levels in both premenopausal and postmenopausal women, whereas in the premenopausal group, E<sub>2</sub> levels were positively correlated with SHBG.

In particular, there appears to be a threshold level for which E<sub>2</sub> is an important determinant of SHBG blood concentrations (25, 26). Among the oophorectomized and nonoophorectomized groups, SHBG levels did not vary with age. The BMI × group interactions resulted in significant findings only in SHBG levels. As presented in Figure 2 and Figure 3, the high postoperative SHBG levels found in the present study are contradictory to some studies that supported a decline in SHBG levels with advancing age (7, 26, 27).

It is noteworthy that even a simple hysterectomy for a benign condition may result in reduced plasma androgens of both ovarian and adrenal origin. Thus, especially hysterectomized premenopausal women should be regularly assessed in terms of these endocrine effects, and more conservative or less radical surgeries should be contemplated. Androgen deficiency in women after natural or surgical menopause may lead to accelerated bone loss, libido loss, and impaired sexual function together with psychological sequelae that adversely affect the quality of life (25). The latter issue is now part of our future research agenda.

In addition to the aforementioned findings, given the short time frame of evaluation, the comparison between oopho-

rectomized and nonoophorectomized groups may be premature and reflect acute vascular insult. Last but not least, a long-duration follow-up is required before making such conclusions regarding the effect of hysterectomy and/or oophorectomy on ovarian androgen production; this merits further research.

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