Hysterectomy, Oophorectomy, and Endogenous Sex Hormone Levels in Older Women: The Rancho Bernardo Study*

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ABSTRACT

This study examines the cross-sectional association of hysterectomy and oophorectomy status, chronological age, and years since menopause with plasma levels of total and bioavailable testosterone and estradiol, androstenedione, estrone, and sex hormone-binding globulin (SHBG) in community-dwelling postmenopausal women who were not using estrogen replacement therapy. Six hundred and eighty-four women, aged 50–89 yr, were surveyed for hysterectomy and oophorectomy status and had plasma obtained between 1984–1987. Of these, 438 (67%) had not undergone hysterectomy or oophorectomy (intact), 123 (18%) reported hysterectomy with bilateral oophorectomy, and 123 (18%) reported hysterectomy with conservation of 1 or both ovaries.

After adjustment for age and body mass index, both total and bioavailable testosterone levels were reduced by more than 40% ($P <$ 0.001) in hysterectomized women with bilateral oophorectomy compared to those in intact women, with intermediate levels observed in hysterectomized women with ovarian conservation. Androstenedione levels were about 10% lower in hysterectomized women with or without ovarian conservation compared to those in intact women ($P =$ 0.039). Total estradiol levels tended to be lower ($P =$ 0.095) in bilat-erally oophorectomized women. Levels of bioavailable estradiol, estrone, and SHBG did not differ by hysterectomy and oophorectomy status.

Among intact women, total, but not bioavailable, testosterone levels increased with age ($P =$ 0.015), reaching premenopausal levels for the 70–79 decade with relatively stable levels thereafter. Among oophorectomized women, total and bioavailable testosterone levels did not vary with age and were 40–50% lower than those in intact women throughout the 50–89 yr age range. Androstenedione levels decreased 27% and SHBG levels increased 30% ($P <$ 0.001) with age in intact, but not oophorectomized, women. Levels of other hormones did not vary with age. Stratification by years since menopause or surgery yielded similar results.

These results demonstrate that the postmenopausal ovary remains a critical source of androgen throughout the lifespan of older women. The clinical consequences of lower testosterone levels years after oophorectomy are unknown. Reconsideration of prophylactic oophorectomy and clinical trials to evaluate the effects of androgen replacement after oophorectomy are needed. (*J Clin Endocrinol Metab* **85:** 645–651, 2000)

H YSTERECTOMY is the second most common major surgical procedure performed in the United States (1); more than one third of U.S. women have had a hysterectomy by age 60 yr, usually performed for benign conditions (2, 3). The highest hysterectomy rates occur in women who are less than 55 yr of age; nevertheless, concomitant bilateral oophorectomy is being performed for 37% of women less than 45 yr of age and for 68% of women aged 45 yr and older (4). Concomitant bilateral oophorectomy is nearly always an elective procedure, recommended to prevent ovarian cancer (5).

Current recommendations for ovarian conservation in women less than 45 yr of age and oophorectomy for women aged 50 yr and older (6) reflect the presumed expendability of the postmenopausal ovary. In a 1994 review, Adashi (7) challenged this position, noting that the postmenopausal ovary is a gonadotropin-driven androgen-producing gland.

More recently, Rako (8) reviewed the possible clinical importance of low androgen levels in oophorectomized women.

Short term studies comparing hormone levels in the ovarian vein and peripheral blood have clearly shown that the postmenopausal ovary is a source of testosterone (9–13). This was confirmed by an early study showing a marked reduction in circulating testosterone levels in postmenopausal women 6–8 weeks after bilateral oophorectomy (14). However, a study of 100 women 1–31 yr after oophorectomy concluded that although testosterone levels were lower in recently oophorectomized women compared to those in intact women, the difference was minimal 5 yr after surgery (15). To our knowledge, no population-based studies have examined endogenous sex hormone levels in older women with respect to their hysterectomy and oophorectomy experiences many years earlier.

In this paper we report the influence of hysterectomy and oophorectomy status, chronological age, and years since menopause on plasma levels of total and bioavailable testosterone and estradiol, androstenedione, estrone, and sex hormone-binding globulin (SHBG) in 684 community-dwelling postmenopausal women who were not using estrogen replacement therapy.

Materials and Methods

Between 1972–1974, 82% of all Caucasian women residing in a middle to upper middle class community in Southern California (Rancho Bernardo) participated in a study of heart disease risk factors. Between 1984–1987, 82% of the surviving, community-dwelling women, aged 50–89 yr, returned to the clinic for another evaluation. At this visit, a standardized interview was used to obtain reproductive and menopausal histories. Postmenopausal women were asked the date of their last menses, type of menopause (natural or surgical), and, in the case of hysterectomy, date and number of ovaries removed at surgery. Because of the older age and the number of years since surgery, medical records to confirm ovarian status were not available for most of the hysterectomized women. Examination of surgical records in a subsample of 228 women from the Rancho Bernardo cohort who reported hysterectomy yielded an overall concordance of 81% for self-reported oophorectomy. There was 96% concordance for women reporting bilateral oophorectomy, whereas medical records of women reporting ovarian conservation showed bilateral oophorectomy in 33%. The reason for hysterectomy or oophorectomy was not ascertained.

Age at menopause was defined as age at last menses for women without hysterectomy and for hysterectomized women whose surgery occurred after natural menopause. For hysterectomized women whose surgery occurred before the cessation of spontaneous menses, age at menopause was defined as 1) age at surgery for bilaterally oophorectomized women, 2) age when estrogen replacement was initiated for women with ovarian conservation, and 3) age 49 yr (the average age of natural menopause in the Rancho Bernardo cohort) for hysterectomized women with ovarian conservation who never used estrogen (31%). Years postmenopause was defined as current age minus age at menopause. Past and current use of estrogen, alone or in combination with a progestin, was ascertained; current estrogen users were excluded from this study. Information regarding current physical activity (exercise three or more times per week), cigarette smoking (yes/no), and alcohol consumption (number of drinks of beer, wine, or liquor converted to milliliters of alcohol per week) was also obtained. Height and weight were measured in the clinic with participants wearing light clothing and no shoes; body mass index (BMI; kilograms per m^2) was used as an estimate of obesity. Blood samples for hormone assay were obtained by venipuncture between 0730–1100 h after a requested 12-h fast; plasma was separated and frozen at −70 C.

Assays were performed on first thawed samples 6–9 yr later, between 1992–1994. Steroid hormone levels were measured by RIA after solvent extraction and Celite column chromatography in the endocrinology research laboratory of S. S. C. Yen (Department of Reproductive Medicine, University of California-San Diego, La Jolla, CA). SHBG levels were determined by the method of Rosner (16), and bioavailable estradiol and testosterone (the non-SHBG-bound fractions) were measured by a method modified from Tremblay and Dube (17). Total estradiol/SHBG and total testosterone/SHBG ratios were used to cross-validate the results obtained for directly measured bioavailable estradiol and testosterone. The sensitivity and the intra- and interassay coefficients of variation, respectively, were 11 pmol/L, 6.0%, and 7.7% for estrone; 11 pmol/L, 5.9%, and 7.1% for estradiol; 11 pmol/L × percentage free, 6.1%, and 7.9% for bioavailable estradiol; 0.07 nmol/L, 4.0%, and 4.9% for testosterone; 0.07 nmol/L × percentage free, 6.5%, and 10.7% for bioavailable testosterone; 0.06 nmol/L, 4.3%, and 4.3% for androstenedione; and 5 nmol/L, 7.5%, and 11.4% for SHBG.

Among the postmenopausal women who were not using estrogen, 696 had steroid hormone and SHBG levels measured. Eight of these women were excluded from the present analysis because their estrogen levels suggested unreported estrogen use, and 3 were excluded on the basis of total testosterone levels more than 2.8 nmol/L. The remaining 684 women are the focus of this report. Of these women, 176 (26%) had estradiol levels and 4 had estrone levels below the sensitivity of the assay; estrogen levels below the sensitivity of the assay were assigned the value of the assay sensitivity. Androgen levels in all subjects were above the assay sensitivity. Hormone and SHBG levels did not vary by season of sampling or duration of storage.

Statistical analysis

Data were analyzed using the SPSS program (SPSS, Inc., Chicago, IL). Hysterectomy and oophorectomy status was stratified into three categories: no hysterectomy or oophorectomy (intact), hysterectomy with conservation of one or both ovaries, and hysterectomy with bilateral oophorectomy. Sex hormone and SHBG levels were stratified by decade of age (50–59, 60–69, 70–79, and 80–89 yr) for intact women and those with bilateral oophorectomy, by years since menopause (<20, 20–30, and >30 yr) for intact women, and by years since surgery for bilaterally oophorectomized women (<20, 20–30, and >30 yr). For statistical analyses, levels of total and bioavailable estradiol and testosterone, androstenedione, and the ratios of estradiol and testosterone to SHBG and of estrone to androstenedione were log-transformed to correct for skewed distributions; antilogs are shown. Other hormones were normally distributed. Significant differences in the number of individuals in each group with hormone levels below the sensitivity of the assay were tested by χ^2 analysis. The relation of hormone and SHBG levels with age, BMI, alcohol consumption, smoking, and exercise was assessed using Pearson correlations. Age- and BMI-adjusted hormone and SHBG levels were compared by hysterectomy and oophorectomy status using analysis of covariance; comparisons by decade of age and by years since menopause or surgery were adjusted for BMI. *Post-hoc* comparisons were performed using Newman-Keuls tests.

Results

Demographic characteristics

The mean age of the 684 women was 73 ± 8 yr (median, 75 yr); 89% were 65 yr of age or older. They were an average of 26 ± 11 yr postmenopause and had a mean BMI of 24.3 ± 3.7 kg/m^2. Overall, 18% (n = 123) reported hysterectomy with conservation of 1 or both ovaries, and 18% (n = 123) reported hysterectomy with bilateral oophorectomy. There were no significant differences by hysterectomy and oophorectomy status for age, BMI, alcohol consumption, current smoking, or exercise (Table 1). Intact women were older at menopause ($P < 0.001$) and had been menopausal for fewer

TABLE 1. Comparison of mean (± SD) age and other covariates by hysterectomy and oophorectomy status for 684 postmenopausal women from the Rancho Bernardo Study, 1984–1987

	Intact (n = 438)	Hysterectomy	
		Ovarian conservation (n = 123)	Bilateral oophorectomy (n = 123)
Age (yr)	74 ± 8	73 ± 9	73 ± 7
BMI (kg/m^2)	24.1 ± 3.7	24.1 ± 3.5	24.5 ± 3.8
Age at menopause (yr)	49 ± 5	45 ± 9[a]	46 ± 9[b]
Yr menopausal	25 ± 10	28 ± 10[b]	28 ± 10[b]
Alcohol consumption (mL/week)	93 ± 109	90 ± 118	89 ± 105
Current smoker (% yes)	31.5	28.2	30.9
Regular exercise (% yes)	17.1	12.9	13.8

[a] $P < 0.001$ *vs.* intact.
[b] $P < 0.05$ *vs.* intact.

TABLE 2. Age- and BMI-adjusted comparisons of mean (± SD) steroid hormone and SHBG levels by hysterectomy and oophorectomy status for 684 postmenopausal women from the Rancho Bernardo Study, 1984–1987

	Intact (n = 438)	Hysterectomy	
		Ovarian conservation (n = 123)	Bilateral oophorectomy (n = 123)
Androstenedione (nmol/L)	1.08 ± 0.39	0.95 ± 0.44	0.99 ± 0.45
Testosterone (nmol/L)	0.56 ± 0.26	0.40 ± 0.20[a]	0.29 ± 0.14[a,b]
Bioavailable testosterone (nmol/L)	0.14 ± 0.07	0.10 ± 0.05[a]	0.08 ± 0.04[a,c]
Testosterone/SHBG ($\times 10^{-3}$)	10.4 ± 6.1	7.4 ± 4.0[a]	6.1 ± 3.6[a]
Estradiol (pmol/L)	18 ± 9	18 ± 7	16 ± 8
Bioavailable estradiol (pmol/L)	9 ± 2	9 ± 3	9 ± 2
Estradiol/SHBG ($\times 10^3$)	0.34 ± 0.20	0.34 ± 0.19	0.34 ± 0.21
Estrone (pmol/L)	70 ± 34	69 ± 39	67 ± 35
SHBG (nmol/L)	62 ± 30	61 ± 29	57 ± 30

Analysis based on log-transformed data for total and bioavailable estradiol and testosterone, androstenedione, testosterone/SHBG, and estradiol/SHBG. Values are antilogs of group means.

[a] $P < 0.001$ *vs.* intact.
[b] $P < 0.001$ *vs.* hysterectomy with ovarian conservation.
[c] $P < 0.01$ *vs.* hysterectomy with ovarian conservation.

years ($P < 0.05$) than hysterectomized women with and without ovarian conservation (Table 1).

Among all women, levels of androstenedione were inversely related and total testosterone and SHBG were positively related to age (all $P < 0.001$). All steroid hormones, except total testosterone and androstenedione, were positively related to BMI ($P < 0.001$ for all); SHBG concentrations were inversely correlated with BMI ($P < 0.001$).

Comparisons by hysterectomy and oophorectomy status

Table 2 shows age- and BMI-adjusted comparisons of hormone and SHBG levels by hysterectomy and oophorectomy status. Androstenedione levels in hysterectomized women were approximately 10% lower than those in intact women ($P = 0.039$) regardless of ovarian status. Compared to those in intact women, total and bioavailable testosterone levels were reduced 29% ($P < 0.001$) in hysterectomized women with ovarian conservation and 40% ($P < 0.001$) in women with bilateral oophorectomy (Fig. 1). Total and bioavailable testosterone levels were 30% lower ($P < 0.001$) in women with bilateral oophorectomy compared to women with ovarian conservation (Fig. 1). Estradiol levels tended to be lower ($P = 0.095$) in women with bilateral oophorectomy than in intact or hysterectomized women with ovarian conservation. A greater ($P = 0.008$) percentage of women with bilateral oophorectomy (37%) had estradiol levels below the sensitivity of the assay compared to intact women (25%) and hysterectomized women with ovarian conservation (23%). Levels of estrone, bioavailable estradiol, SHBG, and the estradiol/SHBG ratio did not differ by ovarian status. The proportion of estradiol (~52%) and testosterone (~26%) not bound to SHBG did not vary by ovarian status (data not shown).

Comparisons by chronological and menopausal age

Among intact women, only androstenedione, total testosterone, and SHBG levels varied with age and years since menopause. Androstenedione levels declined 27% ($P < 0.001$) from the youngest (50–59 yr) to the oldest (80–89 yr) decade (Fig. 2, *left panel*) and were 20% lower ($P < 0.001$) in women more than 30 yr postmenopause (Fig. 2, *right panel*).
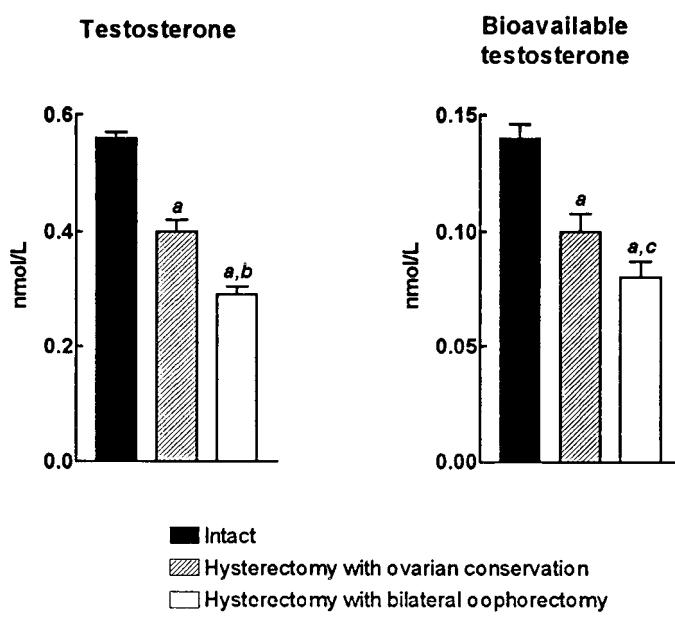

FIG. 1. Age- and BMI-adjusted mean (±SE) total and bioavailable (non-SHBG-bound) testosterone levels by hysterectomy and oophorectomy status in postmenopausal, 50- to 89-yr-old women: intact (n = 438), hysterectomy with ovarian conservation (n = 123), and hysterectomy with bilateral oophorectomy (n = 123). a, $P < 0.001$ *vs.* intact. b, $P < 0.001$; c, $P < .01$ *vs.* hysterectomy with ovarian conservation.

Total testosterone levels increased 35% ($P = 0.015$) with chronological age, with most of the increase occurring after 50–59 yr ($P < 0.01$) and relatively stable levels thereafter (Fig. 3, *left panel*). When examined by years since menopause, testosterone levels were elevated in women 20–30 yr postmenopause compared to those in women less than 20 yr postmenopause ($P < 0.001$) and remained high in women more than 30 yr postmenopause (Fig. 3, *right panel*). As shown in Fig. 3, testosterone levels in the intact women beyond age 70 yr or more than 20 yr post menopause were comparable to published premenopausal levels from the same laboratory (18). Plasma SHBG was positively related to age ($P < 0.001$); levels were 30% higher at 80–89 yr than at 50–59 yr ($P < 0.01$; Fig. 4, *left panel*) and increased progres-

Androstenedione
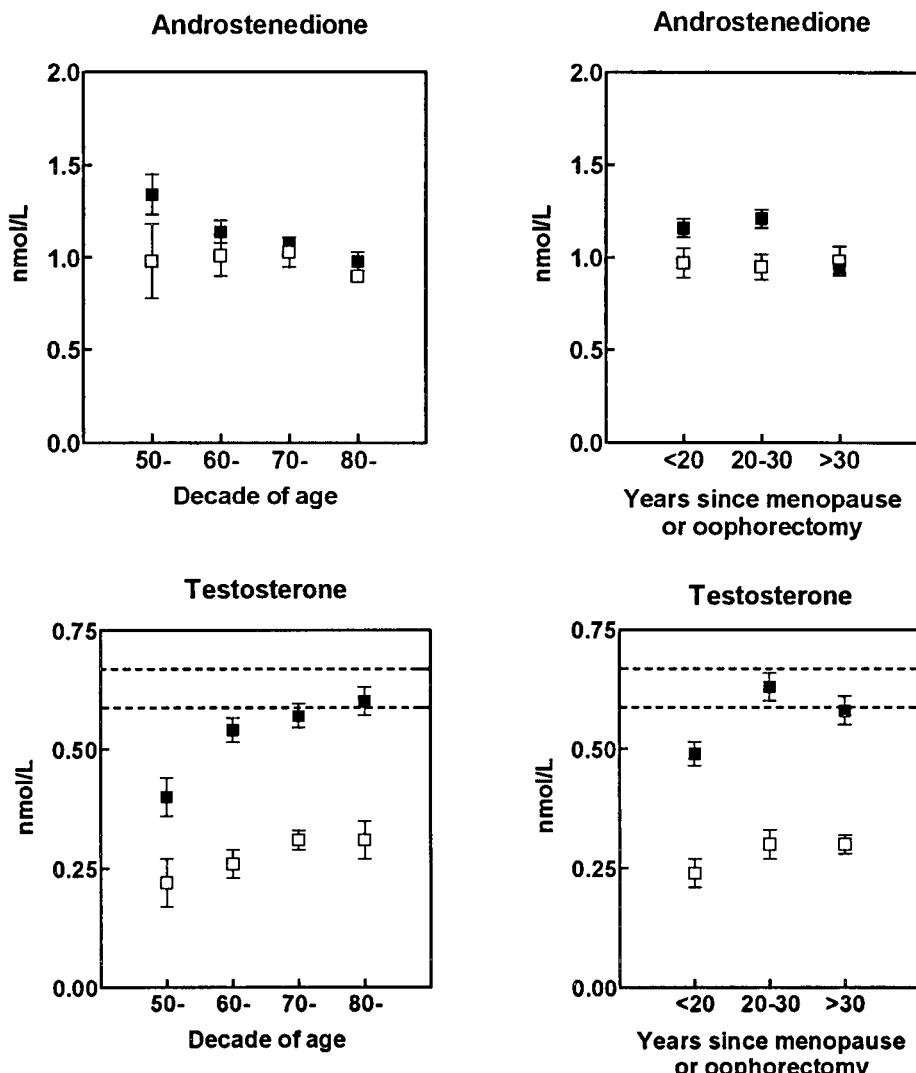
Androstenedione

FIG. 2. BMI-adjusted mean (±SE) androstenedione levels in 438 intact women (*closed squares*) and 123 bilaterally oophorectomized women (*open squares*) stratified by decade of age (*left panel*), and by years since menopause for intact women and years since surgery for oophorectomized women (*right panel*). By decade, n = 29, 80, 231, and 98 for intact and 7, 28, 65, and 23 for oophorectomized. By years since menopause, n = 125, 136, and 119. For years since oophorectomy, n = 49, 27, and 41.

Testosterone

Testosterone

FIG. 3. BMI-adjusted mean (±SE) testosterone levels in 438 intact women (*closed squares*) and 123 bilaterally oophorectomized women (*open squares*) stratified by decade of age (*left panel*) and by years since menopause for intact women and years since surgery for oophorectomized women (*right panel*). *Dotted lines* indicate the mean (±SE) testosterone level for premenopausal women (from Ref. 36). See Fig. 2 for numbers of subjects after stratification.

sively ($P < 0.001$) when stratified by duration of menopause (Fig. 4, *right panel*). Among oophorectomized women, hormone and SHBG levels did not vary with age or years since surgery (Figs. 2–5). Both total (Fig. 3) and bioavailable (Fig. 5) testosterone levels were 40–50% lower in oophorectomized than intact women throughout the 50- to 89-yr age range.

Estrone to androstenedione ratio: aromatase activity

The ratio of estrone to androstenedione (E_1/A) was examined as an index of aromatase activity. The E_1/A ratio did not differ on the basis of ovarian status (data not shown) and was correlated to BMI for both intact (r = 0.21) and oophorectomized (r = 0.37) women ($P < 0.001$ for each). In age-stratified analyses, the BMI-adjusted E_1/A ratio was similar in intact and oophorectomized women and increased progressively with age in both groups ($P < 0.001$; data not shown).

Lifestyle covariates

Age- and BMI-adjusted partial correlations revealed that only androstenedione levels were positively related to alco-

hol consumption and current smoking (r = 0.15; $P < 0.001$ for each); SHBG levels were inversely associated with alcohol consumption (r = −0.12; $P = 0.006$). Neither hormone nor SHBG levels were associated with reported physical activity. Adjusting for alcohol consumption, current smoking, or exercise did not significantly alter any hormone associations with hysterectomy and oophorectomy status, chronological age, or years since menopause or surgery (data not shown).

Discussion

Between 1988–1990, more than half a million women per yr in the United States had a hysterectomy, and 50% of these women had both ovaries removed at that time (4). Given the increasing life expectancy of women and the frequency of bilateral oophorectomy, determining the role of the ovary in older women's health is important (8, 19). In this, the first community-based study to examine the relation of remote hysterectomy with and without oophorectomy to endogenous sex hormone levels in older women, bilateral oophorectomy had little or no effect on circulating estrogen levels in older women, but was associated with a substantial and sustained reduction in total and bioavailable testosterone
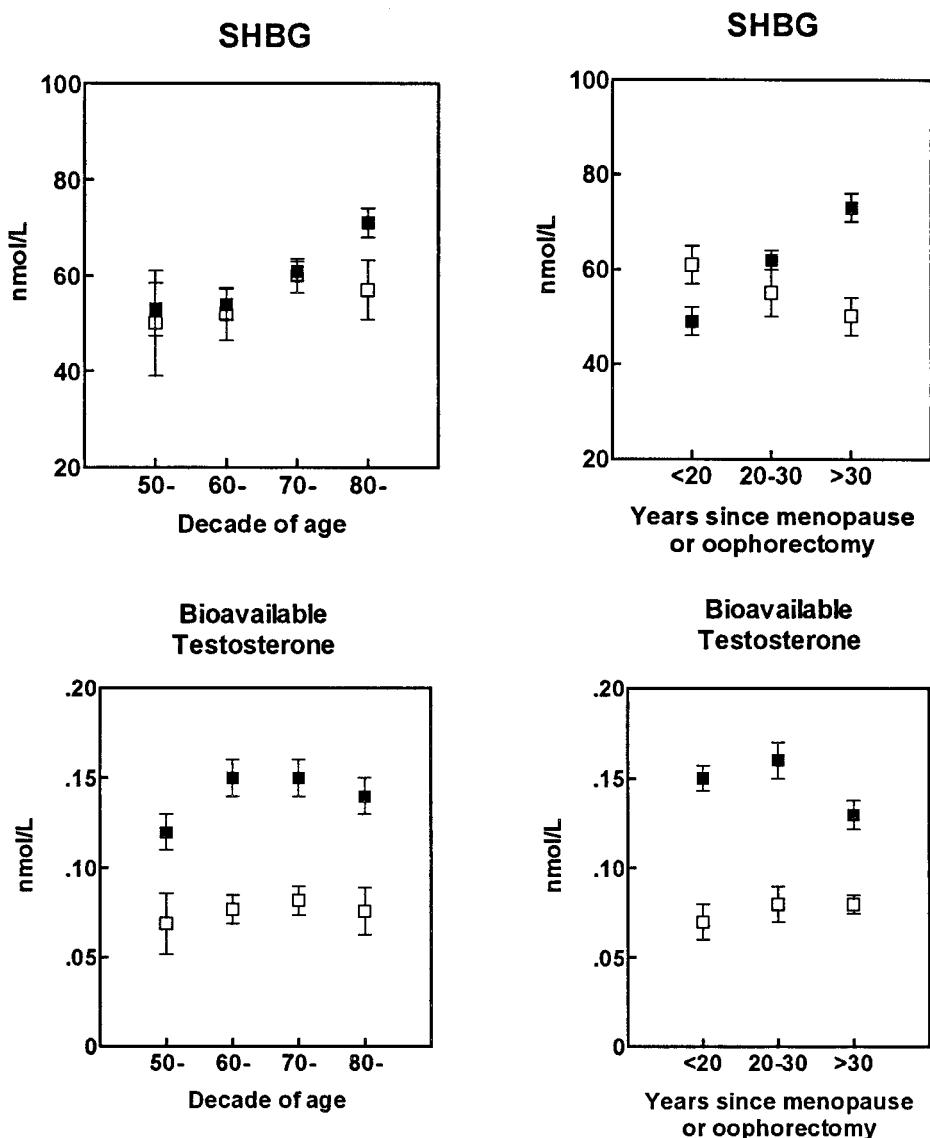
SHBG

FIG. 4. BMI-adjusted mean (±SE) SHBG levels in 438 intact women (*closed squares*) and 123 bilaterally oophorectomized women (*open squares*) stratified by decade of age (*left panel*) and by years since menopause for intact women and years since surgery for oophorectomized women (*right panel*). See Fig. 2 for the numbers of subjects after stratification.

Bioavailable Testosterone

FIG. 5. BMI-adjusted mean (±SE) bioavailable testosterone levels in 438 intact women (*closed squares*) and 123 bilaterally oophorectomized women (*open squares*) stratified by decade of age (*left panel*) and by years since menopause for intact women and years since surgery for oophorectomized women (*right panel*). See Fig. 2 for the numbers of subjects after stratification.

levels. In contrast, although testosterone levels were low around the time of menopause, an apparent increase in ovarian testosterone production and a return to premenopausal levels occurred in intact women.

Fifty percent of the hysterectomized women in this cohort reported concomitant bilateral oophorectomy, in accord with the national rate (4). Androstenedione levels for these women were 15% lower and testosterone levels were 40% lower than those in intact women, in agreement with early small studies by Judd *et al.* (14) and Vermeulen (20). That these differences directly reflect ovarian androgen production is substantiated by higher androgen levels in the ovarian than the peripheral veins of menopausal women (9–12). To our knowledge, this is the first study to report that directly measured bioavailable (non-SHBG-bound) testosterone levels are also reduced 40% in oophorectomized postmenopausal women. This is apparently a direct effect of the lower testosterone levels, because neither SHBG levels nor the proportion of testosterone not bound to SHBG varied by ovarian status. Others have noted that the major factor in determin-

ing bioavailable testosterone levels in women is the total testosterone level (21). Thus, the ovary plays a critical role in determining both the circulating level and the bioactivity of testosterone in postmenopausal women.

Testosterone levels were also reduced, although to a lesser extent, in hysterectomized women with ovarian conservation. There are two potential explanations for this finding. Damage to the ovarian artery at the time of hysterectomy may lead to functional impairment or failure of one or both ovaries (22, 23). Alternatively, mistaken inclusion of bilaterally oophorectomized women in the hysterectomy with ovarian conservation group is plausible; hospital records, available for a subset of this cohort, showed that 33% of women who reported hysterectomy did not know that both their ovaries had been removed. In contrast, reported bilateral oophorectomy was confirmed in 96% of cases.

These data also demonstrate that the impact of oophorectomy on testosterone levels is sustained; total and bioavailable testosterone levels in oophorectomized women were 40–50% lower than those in intact women throughout older

age independent of age at surgery. The only other study reporting sex hormone levels in postmenopausal women many years after oophorectomy did not observe a consistent reduction in testosterone levels 1–31 yr postsurgery (15). The small numbers of women at each time interval and the relatively unsophisticated assay techniques available in this early study may account for these discordant results.

The MCRs and interconversion rates of androgens in women are not altered with aging (24); therefore, changes in circulating levels in older women must reflect alterations in either adrenal or ovarian secretion. In this study, total testosterone levels increased and androstenedione levels declined with age and years since menopause in intact, but not oophorectomized, women. Among intact women, testosterone levels in the youngest chronological and menopausal age groups were 30% lower than published values for premenopausal women from the same laboratory (18), whereas levels in women more than 70 yr of age or 20 yr postmenopause were comparable to premenopausal levels. These results are compatible with a decline in ovarian testosterone production around the time of menopause, followed by increased ovarian synthesis and restoration of premenopausal levels. Longitudinal studies support this interpretation; two studies (25, 26) spanning the menopausal transition reported a perimenopausal drop in testosterone levels of about 20%, with increasing levels in the following 2 yr (26). Another (27) observed increasing testosterone levels in 32 women sampled every 3–6 months during the 10 yr immediately after menopause. Our findings are also in general agreement with a cross-sectional study of 60 postmenopausal women by Chakravarti *et al.* (28) in which testosterone levels were 25% higher in women 20–30 yr post menopause at a time when androstenedione levels were falling. Bancroft and Cawood (29), however, found a negative relation between age and androstenedione in women 40–60 yr of age, and other smaller cross-sectional studies (20, 30–33) across a narrower age range (33) observed no significant changes with advancing age for either androstenedione or testosterone.

Estrone and bioavailable estradiol levels were not related to ovarian status, and only a weak ($P = 0.095$) association was seen with total estradiol levels, consistent with the idea that postmenopausal circulating estrone and estradiol levels are derived primarily from peripheral aromatization of androstenedione and testosterone (for review, see Ref. 34). This study confirms previous findings (20, 29–32) showing that estrogen levels are unaffected by chronological or menopausal aging. Aromatase activity and its positive relation with age and adiposity (24, 35, 36) were unaltered in the oophorectomized women; thus, remote oophorectomy does not seem to influence peripheral estrogen production in older women.

Overall, SHBG levels were not influenced by ovarian status; however, an age-associated increase in levels was seen in intact, but not oophorectomized, women. The reason for this unexpected finding is unknown. Two previous studies reported a positive relationship between age and SHBG levels in women (37, 38), similar to that identified for men (38–40). Age-related changes in testosterone, insulin, and adiposity do not account for the increase in SHBG with age, as all have an inhibitory influence on SHBG (41). Insulin-like growth factor I and SHBG levels are inversely related in both men and women (39, 40), and IGF-I inhibits hepatic production of SHBG *in vitro* (42–44). Thus, a decline in the inhibiting effect of IGF-I with age could contribute to increased SHBG levels in both men and intact women, although this does not explain the absent increase in oophorectomized women.

This study has a number of limitations. Hormone levels were based on a single morning sample. Although single measurements of most plasma hormones have been shown to characterize average levels in postmenopausal women reliably over a 2- to 3-yr period, estrogen levels are not as reproducible (45–47). Thus, estrogen levels and associations (or lack of them) should be viewed with caution. Changes in hormone levels during long term storage were unlikely to explain observed associations; hormone levels were measured in never previously thawed plasma, and levels did not vary by season of sampling or duration of storage. In addition, others have shown that levels of steroid hormones are relatively stable in frozen plasma stored for 3–10 yr (48, 49). Finally, although age-specific levels were based on relatively few women for the youngest decade, the similarity of hormone patterns after stratification by decade and years since menopause supports the validity of the age-related associations.

The reduction in testosterone levels in intact women during early postmenopause and the sustained reduction of both total and bioavailable testosterone in bilaterally oophorectomized women of all ages may have important clinical significance, especially for skeletal health. Androgens inhibit bone resorption as well as increasing bone formation (50, 51), and low levels of endogenous testosterone have been reported to correlate with fractures in elderly women (52, 53). During the perimenopause, women with higher testosterone concentrations have slower rates of bone loss than those with lower concentrations independent of their estrogen status (54). Clinical trials have shown that androgens act synergistically with estrogens in surgically and naturally menopausal women to relieve vasomotor symptoms, increase bone mineral density, and enhance libido, well-being, and energy level (55–60). Although further studies are needed, the testosterone data from this study may help in determining whether, when, and for how long androgen replacement should be recommended for menopausal women.

In summary, the results of this study demonstrate that the postmenopausal ovary is a critical source of androgen throughout the lifespan of older women. Although testosterone levels are low around the time of menopause, an apparent increase in ovarian testosterone production and a return to premenopausal levels occur in intact women. In contrast, bilateral oophorectomy results in a pronounced and sustained reduction in both total and bioavailable testosterone levels. The consequences of the lower testosterone levels many years after oophorectomy for the health and well-being of aging women are unknown. Reconsideration of prophylactic oophorectomy and clinical trials to evaluate the effects of androgen replacement after oophorectomy are needed.

References

1. **National Center for Health Statistics.** 1994 Health United States. Hyattsville: Public Health Service.

2. **Greenwood S.** 1988 Hysterectomy and ovarian removal: a major health issue in the perimenopausal years. West J Med. 149:771–772.
3. **Pokras R, Hufnagel VG.** 1988 Hysterectomy in the United States, 1965–84. Am J Public Health. 78:852–853.
4. **Wilcox LS, Koonin LM, Pokras R, Strauss LT, Zhisen X, Peterson HB.** 1994 Hysterectomy in the United States, 1988–1990. Obstet Gynecol. 83:549–555.
5. **Sightler SE, Boike GM, Estape RE, Averette HE.** 1991 Ovarian cancer in women with prior hysterectomy: a 14-year experience at the University of Miami. Obstet Gynecol. 78:681–684.
6. **Carlson KJ, Nichols DH, Schiff I.** 1993 Indications for hysterectomy. N Engl J Med. 328:856–860.
7. **Adashi EY.** 1994 The climacteric ovary as a functional gonadotropin-driven androgen-producing gland. Fertil Steril. 62:20–27.
8. **Rako S.** 1998 Testosterone deficiency; a key factor in the increased cardiovascular risk to women following hysterectomy or with natural aging? J Women's Health. 7:825–829.
9. **Judd HL, Judd GE, Lucas WE, Yen SSC.** 1974 Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab. 39:1020–1024.
10. **Lucisano A, Acampora MG, Russo N, Maniccia E, Montemurro A, Dell'Acqua S.** 1984 Ovarian and peripheral plasma levels of progestogens, androgens, and oestrogens in post-menopausal women. Maturitas. 6:45–53.
11. **Aiman J, Forney JP, Parker Jr CR.** 1986 Secretion of androgens and estrogens by normal and neoplastic ovaries in postmenopausal women. Obstet Gynecol. 68:1–5.
12. **Sluijmer AV, Heineman MJ, De Jong FH, Evers JLH.** 1995 Endocrine activity of the postmenopausal ovary: the effects of pituitary down-regulation and oophorectomy. J Clin Endocrinol Metab. 80:2163–2167.
13. **Longcope C, Hunter R, Franz C.** 1980 Steroid secretion by the postmenopausal ovary. Am J Obstet Gynecol. 138:564–568.
14. **Judd HL, Lucas WE, Yen SSC.** 1974 Effect of oophorectomy on circulating testosterone and androstenedione levels in patients with endometrial cancer. Am J Obstet Gynecol. 38:793–798.
15. **Studd JWW. Chakravarti S, Collins WP.** 1978 Plasma hormone profiles after the menopause and bilateral oophorectomy. Postgrad Med J. 54(Suppl 2):25–30.
16. **Rosner W.** 1972 A simplified method for the quantitative determination of testosterone-estradiol-binding globulin activity in human plasma. J Clin Endocrinol Metab. 34:983–988.
17. **Tremblay RR, Dube JY.** 1974 Plasma concentrations of free and non-TeBG bound testosterone in women on oral contraceptives. Contraception. 10:599–605.
18. **Arroyo A, Laughlin GA, Morales AJ, Yen SCC.** 1997 Inappropriate gonadotropin secretion in polycystic ovary syndrome: influence of adiposity. J Clin Endocrinol Metab. 82:3728–3733.
19. **Plouffe L Jr.** 1998 1998 Ovaries, androgens and the menopause: practical applications. Semin Reprod Endocrinol 16:117–20.
20. **Vermeulen A.** 1976 The hormonal activity of the postmenopausal ovary. J Clin Endocrinol Metab. 42:247–253.
21. **Cumming DC, Wall SR.** 1985 Non-sex hormone-binding globulin-bound testosterone as a marker for hyperandrogenism. J Clin Endocrinol Metab. 61:873–876.
22. **Riedel H, Lehmann-Willenbrock E, Semm K.** 1986 Ovarian failure phenomenon after hysterectomy. J Reprod Med. 31:597–600.
23. **Pete I, Bosze P.** 1998 The fate of the retained ovaries following radical hysterectomy. Eur J Gynaecol Oncol. 19:22–24.
24. **Longcope C, and Baker S.** 1993 Androgen and estrogen dynamics: relationships with age, weight, and menopausal status. J Clin Endocrinol Metab. 76:601–604.
25. **Rannevik G, Jeppsson S, Johnell O, Bjerre B, Laurell-Borulf Y, Svanberg L.** 1995 A longitudinal study of the perimenopausal transition: altered profiles of steroid and pituitary hormones, SHBG and bone mineral density. Maturitas. 21:103–113.
26. **Overlie I, Moen MH, Morkrid L, Skjaeraasen, Holte A.** 1999 The endocrine transition around menopause: a five years prospective study with profiles of gonadotropins, estrogens, androgens and SHBG among healthy women. Acta Obset Gynecol Scand. 78:642–647.
27. **Jiroutek MR, Chen M-H, Johnston CC, Longcope C.** 1998 Changes in reproductive hormones and sex hormone-binding globulin in a group of postmenopausal women measured over 10 years. Menopause. 5:90–94.
28. **Chakravarti S, Collins WP, Forecast JD, Newton JD, Oran DH, Studd JWW.** 1976 Hormonal profiles after the menopause. Br Med J. 2:784–787.
29. **Bancroft J, Cawood EH.** 1996 Androgens and the menopause; a study of 40–60-year-old women. Clin Endocrinol (Oxf). 45:577–587.
30. **Meldrum DR, Davidson BJ, Tataryn IV, Judd HL.** 1981 Changes in circulating steroids with aging in postmenopausal women. Obstet Gynecol. 57:624–628.
31. **Vermeulen A, Verdonck L.** 1979 Factors affecting sex hormone levels in postmenopausal women. J Steroid Biochem. 11:899–904.
32. **Labrie F, Belanger A, Cusan L, Gomez J-L, Candas B.** 1997 Marked decline in serum concentrations of adrenal C19 sex steroid precursors and conjugated androgen metabolites during aging. J Clin Endocrinol Metab. 82:2396–2402.
33. **Cauley JA, Gutal JP, Kuller LH, LeDonne D, Powell JG.** 1989 The epidemiology of serum sex hormones in postmenopausal women. Am J Epidemiol. 129:1120–1131.
34. **Yeh J, Adashi EY.** 1999 The ovarian life cycle. In: Yen SSC, Jaffe RB, Barbieri RL, eds. Reproductive endocrinology, 4th Ed. Philadelphia: Saunders;153–191.
35. **Cleland WH, Mendelson CR, Simpson ER.** 1985 Effects of aging and obesity on aromatase activity of human adipose cells. J Clin Endocrinol Metab. 60:174–177.
36. **Bulen SE, Simpson ER.** 1994 Competitive reverse transcription-polymerase chain reaction analysis indicates that levels of aromatase cytochrome P450 transcripts in adipose tissue of buttocks, thighs, and abdomen of women increase with advancing age. J Clin Endocrinol Metab. 78:428–432.
37. **Kwekkeboom DJ, de Jong FH, van Hemert AM, Vandenbroucke JP, Valkenburg HA, Lamberts SWJ.** 1990 Serum gonadotropins and α-subunit decline in aging normal postmenopausal women. J Clin Endocrinol Metab. 70:944–950.
38. **Maruyama Y, Aoki N, Suzuki Y, Sinohara H, Yamamoto T.** 1984 Variation with age in the levels of sex-steroid-binding plasma protein as determined by radioimmunoassay. Acta Endocrinol (Copenh). 106:428–432.
39. **Pfeilschifter J, Scheidt-Nave C, Leidig-Bruckner, et al.** 1996 Relationship between circulating insulin-like-growth factor components and sex hormones in a population-based sample of 50- to 80-year-old men and women. J Clin Endocrinol Metab. 81:2534–2540.
40. **Vermeulen A, Kaufman JM, Giagulli VA.** 1996 Influence of some biological indexes on sex hormone-binding globulin and androgen levels in aging or obese males. J Clin Endocrinol Metab. 81:1821–1826.
41. **Rosner W.** 1990 The functions of corticosteroid-binding globulin and sex hormone-binding globulin: recent advances. Endocr Rev. 11:80–91.
42. **Singh A, Hamilton-Farley D, Koistenen R, et al.** 1990 Effects of insulin-like growth factor-type 1 (IGF-I) and insulin on the secretion of sex hormone binding globulin and IGF-I binding protein (IBP-I) by human hepatoma cells. J Endocrinol. 124:R1–R3.
43. **Plymate SR, Hoop RC, Jones RE, Matej LA.** 1990 Regulation of sex hormone-binding globulin production by growth factors. Metabolism. 39:967–970.
44. **Crave JC, Lejeune H, Brebant C, Baret C, Pugeat M.** 1995 Differential effects of insulin and insulin-like growth factor 1 on the production of plasma steroid-binding globulins by human hepatoblastoma-derived (Hep G2) cells. J Clin Endocrinol Metab. 80:1283–1289.
45. **Hankinson SE, Manson JE, Spiegelman D, Willett WC, Longcope C, Speizer FE.** 1995 Reproducibility of plasma hormone levels in postmenopausal women over a 2–3 year period. Cancer Epidemiol Biomarkers Prev. 4:649–654.
46. **Cauley JA, Gutai JP, Kuller LH, Powell JG.** 1991 Reliability and interrelations among serum sex hormones in postmenopausal women. Am J Epidemiol. 133:50–57.
47. **Muti P, Trevisan M, Micheli A, Krogh V, Bolelli G, Siajno R, Berrino F.** 1996 Reliability of serum hormones in premenopausal and postmenopausal women over a one-year period. Cancer Epidemiol Biomarkers Prev. 5:917–922.
48. **Bolelli G, Muti P, Micheli A, et al.** 1995 Validity for epidemiological studies of long-term cryoconservation of steroid and protein hormones in serum and plasma. Cancer Epidemiol Biomarkers Prev. 4:509–13.
49. **Kley HK, Schlaghecke R, Kruskemper HL.** 1985 Stability of steroids in plasma over a 10-year period. J Clin Chem Clin Biochem. 23:875–878.
50. **Raisz LG, Wiita B, Artis A, et al.** 1996 Comparison of the effects of estrogen alone and estrogen plus androgen on biochemical markers of bone formation and resorption in postmenopausal women. J Clin Endocrinol Metab. 81:37–43.
51. **Baran DT, Bergfeld MA, Teitelbaum SL, et al.** 1978 Effect of testosterone therapy on bone formation in an osteoporotic male. Calif Tissue Res. 26:103–106.
52. **Longcope C, Baker RS, Hui SL, Johnston Jr CC.** 1984 Androgen and estrogen dynamics in women with vertebral crush fractures. Maturitas. 6:309–318.
53. **Davidson BJ, Ross RK, Paganini-Hill A, Hammond GD, Siiteri PK, Judd HL.** 1982 Total and free estrogens and androgens in postmenopausal women with hip fractures. J Clin Endocrinol Metab. 54:115–120.
54. **Slemenda C, Hui SL, Longcope C, Johnston CC.** 1987 Sex steroids and bone mass. A study of changes about the time of menopause. J Clin Invest. 80:1261–1269.
55. **Davis SR, McCloud P, Strauss BJ, Burger H.** 1995 Testosterone enhances estradiol's effects on postmenopausal bone density and sexuality. Maturitas. 21:227–236.
56. **Sherwin BB, Gelfand MM, Brender W.** 1985 Androgen enhances sexual motivation in females: a prospective, crossover study of sex steroid administration in the surgical menopause. Psychosom Med. 47:339–351.
57. **Watts NB, Notelovitz M, Timmons MC, Addison WA, Wiita B, Downey LJ.** 1995 Comparison of oral estrogens and estrogens plus androgen on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. Obstet Gynecol. 85:529–537.
58. **Erdtsieck RJ, Pols HA, van Kuijk C, Birkenhager-Frenkel DH, et al.** 1994 Course of bone mass during and after hormonal replacement therapy with and without addition of nandrolone decanoate. J Bone Miner Res. 9:277–283.
59. **Sarrel P, Dobay B, Wiita B.** 1998 Estrogen and estrogen-androgen replacement in postmenopausal women dissatisfied with estrogen-only therapy. Sexual behavior and neuroendocrine responses. J Reprod Med. 43:847–856.
60. **Barrett-Connor E, Young R, Notelovitz M, Sullivan J, et al.** 1999 A two-year, double-blind comparison of estrogen-androgen and conjugated estrogens in surgically menopausal women. J Reprod Med. 44:1012–1020.