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The Postmenopausal Ovary Is Not a Major Androgen-Producing Gland

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It is currently believed that the postmenopausal ovary remains a gonadotropin-driven, androgen-producing gland. However, the adrenal contribution to circulating androgen levels may explain some conflicting results previously reported. In addition, the steroidogenic potential and gonadotropin responsiveness of the postmenopausal ovary have not been recently reassessed. Plasma T, bioavailable T, free T, androstenedione (Adione), and dehydroepiandrosterone sulfate levels were measured in postmenopausal or ovariectomized women with complete adrenal insufficiency, compared with women with intact adrenals. A stimulation human chorionic gonadotropin test (on d 0, 3, and 6) was performed in postmenopausal women with adrenal insufficiency. Dexamethasone was administered for 4 d in postmenopausal women with intact adrenals. Intraovarian T and androstenedione were also measured in homogenates of ovarian tissue from postmenopausal women. Immunocytochemistry was performed on postmenopausal ovaries and premenopausal controls to detect the presence of steroidogenic enzymes (P-450 aromatase, P-450 SCC, 3β HSD, and P-450 C17) and gonadotropin receptors. Plasma androgen levels were below or close to the limit of the assay in all women with adrenal insufficiency. They were similar in postmenopausal and oophorectomized women with normal adrenals. No hormonal changes were observed after human chorionic gonadotropin injections in women with adrenal insufficiency. In contrast, a dramatic decrease of all steroids was observed after dexamethasone administration in postmenopausal women with intact adrenals. Intraovarian T and androstenedione levels were negligible in postmenopausal ovarian tissue. P-450 aromatase was absent from the 17 ovaries studied, and the enzymes for androgen biosynthesis were either absent (n = 13) or present in very low amounts (n = 4). In all the postmenopausal ovaries, FSH and LH receptors were completely absent. In the absence of adrenal steroids, postmenopausal women have no circulating androgens. This result is consistent with the immunocytochemical studies showing the almost constantly absent steroidogenic enzymes and LH receptors in the postmenopausal ovary. Thus, the climacteric ovary is not a critical source of androgens. The arrest of androgen secretion after menopause may impact significantly on women's health. (*J Clin Endocrinol Metab* 86: 5060–5066, 2001)

THERE IS SUBSTANTIAL evidence that androgens may play a role in postmenopausal women's quality of life (1–4). In the postmenopausal ovary, the loss of ovarian follicles and granulosa cells eliminates its E-producing capabilities. However, according to the classification of Erickson *et al.* (5), secondary interstitial cells, direct descendants of theca interstitial cells of atretic follicles, and hilar cells, similar to testicular Leydig cells, may persist in the postmenopausal ovary. It has been thought for many years that these cells, continuously activated by the high levels of circulating LH, are steroidogenically active (6). Thus, it is currently believed that, after menopause, the ovaries are a major site of androgen production. However, the persistent adrenal contribution may explain some conflicting results previously reported (6–13).

The aim of the present investigation was to further assess the steroidogenic potential and gonadotropin responsiveness of the postmenopausal ovary. To eliminate adrenal androgen contribution, postmenopausal women with adrenal insufficiency were studied. In addition, T and androstenedione (Adione) were measured directly in postmenopausal ovarian tissue homogenates. Finally, immunocytochemical studies were performed to analyze the presence of steroidogenic enzymes and gonadotropin receptors. The results demonstrate that the climacteric ovary is not a major androgen-producing gland.

Abbreviations: BMI, Body mass index; DHEAS, dehydroepiandrosterone sulfate; DXM, dexamethasone; hCG, human chorionic gonadotropin; LHR, LH receptor.

Subjects and Methods

Subjects

Ten postmenopausal women, aged 50–75 yr, with complete adrenal insufficiency participated in the study. Postmenopause was defined by elevated plasma gonadotropin levels, plasma inhibin B, and E2 levels below 10 pg/ml and 5 pg/ml, respectively. Five patients had Addison's disease owing to adrenal tuberculosis recognized radiologically by calcifications of the adrenals and/or the absence of cytochrome P-450 C21 hydroxylase antibodies. Five patients had Cushing's disease treated 20–30 yr before the present study by bilateral total adrenalectomy. Adrenal insufficiency was confirmed by plasma cortisol and aldosterone levels below 1 μg/dl and 15 pg/ml, respectively. Plasma ACTH and renin levels were increased. Three women, aged 45–69 yr, with adrenal insufficiency (two with Addison's disease and one with Cushing's disease treated by bilateral adrenalectomy) previously ovariectomized for benign gynecological disorders were also studied. Controls consisted of 15 postmenopausal women, aged 45–81 yr, and 15 ovariectomized women, aged 46–76 yr. Both control groups had intact adrenal function. Body mass index (BMI) and duration of menopause or time after ovariectomy were similar between the two control groups and women with adrenal insufficiency (Table 1). All patients and controls were studied after withdrawal of hormone replacement therapy for at least 3 months preceding the investigation. Treatment with hydrocortisone and mineralocorticoids were maintained in patients with adrenal insufficiency.

TABLE 1. Characteristics of postmenopausal and ovariectomized women with adrenal insufficiency (POSTM + AI, OVX + AI) or with intact adrenals (POSTM, OVX)

Characteristics	POSTM + AI	OVX + AI	POSTM	OVX
Age (yr)				
Mean	56 ± 4	55 ± 7	57 ± 4	53 ± 3
Range	50–75	45–69	45–81	46–76
BMI				
Mean	23.9	23.8	24.8	24.3
Range	19.9–28.1	21.1–27.2	20.2–30.1	19.8–29.9
Years since menopause or ovariectomy				
Mean	12.9 ± 4	14.6 ± 4.4	13.3 ± 2.0	15.3 ± 2.1
Range	5.0–26.8	6.0–20.0	5.0–35.0	5.0–31.0

Whole ovarian tissues (containing the hilus) were obtained from 17 postmenopausal patients (aged 50–70 yr) 5–20 yr after menopause undergoing hysterectomy and bilateral salpingo-oophorectomy. None of the patients had received E treatment (less than 3 months) before surgery. Eight ovarian samples were obtained for comparison from eight normally cycling women, aged 42–50 yr, undergoing unilateral salpingo-oophorectomy for benign gynecological pathology.

The study was approved by the local investigation committee.

Protocol

Plasma levels of total T, bioavailable T, free T, Adione, and dehydroepiandrosterone sulfate (DHEAS) were measured in all the postmenopausal or ovariectomized patients with adrenal insufficiency or intact adrenal function at baseline.

A human CG (hCG) stimulation test was performed in the 10 postmenopausal women with adrenal insufficiency by administration of an im bolus of 5000 IU at 0800 h on d 0, 3, and 6. Plasma T and Adione were measured every 4 h for the first 72 h and every 24 h after the two additional injections of hCG.

Dexamethasone (DXM; 1 mg twice daily for 4 d) was administered in the group of postmenopausal women with normal adrenal function, and plasma levels of T, Adione, and DHEAS were measured before the study began and on d 5.

Hormone assays

Plasma T, bioavailable T, free T, Adione, and DHEAS levels were measured in duplicate using established RIAs as previously described (14, 15). The intra- and interassay variations were 15% and 17%, respectively, for T at the concentration of 20 ng/dl. The limit of sensitivity of the assay was 5 ng/dl for T and 1 ng/dl for bioavailable T. The intra- and interassay coefficients of variation for free T were 15% and 17% at the concentration of 30 pg/dl with a limit of sensitivity of the assay of 15 pg/dl. The intra- and interassay variations were 7% and 11%, respectively, for Adione at the concentration of 80 ng/dl. The limit of sensitivity of the assay was 10 ng/dl. Intra- and interassay coefficients of variation for DHEAS were 3.2% and 8%, respectively, for a concentration of 50 μg/dl. The limit of sensitivity of the assay was 2 μg/dl.

Intraovarian measurement of T and Adione in ovarian tissue homogenates

Whole ovarian tissues containing the hilus from five postmenopausal and three premenopausal women were dissected, immediately pulverized with a Thermovac apparatus (Fisher Scientific Laboratories, Elancourt, France). They were transferred and homogenized at 0–4 C in a Teflon-glass Potter homogenizer, with 6 volumes Tris buffer (10 nM/liter Tris/liter, 1.5 mM EDTA/liter, 0.5 mM dithiothreitol/liter, and HCL) (pH 7.4) containing serum albumin (BSA 5 g/liter) at 0 C. Cytosol was obtained by centrifugation at 10,5000 × *g* for 65 min at 0 C.

T and Adione levels were measured in the whole homogenates with the same RIAs described above.

Immunocytochemistry

Seven of the 17 postmenopausal ovaries were snap-frozen in liquid nitrogen after removal, and 10 were fixed in buffered formol and paraffin embedded. The ovarian samples obtained from the eight cycling women were processed similarly (four frozen and four formol-fixed) and used as controls.

The frozen ovaries were sectioned at 6-μm thickness and fixed in −20 C acetone for 5 min. The paraffin sections were deparaffinized and microwaved for 15 min at full power in citrate buffer (pH 6) and immunostained at 4 C overnight with anti-P-450 aromatase, -P-450 SCC, -3β HSD, and -P-450 C17 antibodies at the respective dilutions of 1:6,000, 1:6,000, 1:10,000 and 1:1,000 for the frozen sections and 1:3,000, 1:3,000 1:6,000 and 1:750 for the paraffin sections (16–19). The bound immunoglobulins were revealed with biotinylated antibodies and streptavidin-peroxidase LSAB2 kit (DAKO Corp., Santa Barbara, CA). Aminoethylcarbazole was used as a chromogen, and the sections were counterstained with hematoxylin. Mouse immunoglobulins, preimmune rabbit immunoglobulins, and an irrelevant rabbit polyclonal antibody (Anti Von Willebrand factor, DAKO Corp.) were used as negative controls.

The preparation, purification, and specificity tests of the anti-FSH and anti-LH receptor (LHR) monoclonal antibodies, used to label the seven frozen ovaries, have been previously published (16, 17) The sections were incubated with three antibodies recognizing three different epitopes of the extracellular domain of the LHR (LHR 29, LHR 1055, and LHR 74) at the respective dilutions of 10, 10, and 5 μg/ml and with the anti-FSH receptor antibody 323, at the concentration of 5 μg/ml (16).

Statistical analysis

Comparisons of basal values between postmenopausal or ovariectomized women with adrenal insufficiency or with intact adrenals were made with the Wilcoxon test, after adjusting for age and BMI. The value of the limit of the assay was used for the undetectable levels. Basal values and values after hCG stimulation in postmenopausal women with adrenal insufficiency and values before and after DXM test in postmenopausal women with intact adrenals were made with the Wilcoxon's signed rank test for matched pairs. Comparisons of percentage of cells between postmenopausal ovaries and controls were made with the Wilcoxon test. Statistical significance was assumed for P less than 0.05.

Results

Steroid concentrations in plasma and ovaries

In the postmenopausal women with adrenal insufficiency, the plasma levels of total T, bioavailable T, and free T were undetectable, below the limit of the assay. The plasma levels were also undetectable in ovariectomized women with adrenal insufficiency (Fig. 1). In the postmenopausal women with intact adrenals, the plasma levels of total T, bioavailable T, and free T were 18 ± 2 ng/dl, 3.7 ± 0.6 ng/dl, and 30 ± 6 pg/dl, respectively (Fig. 1). In the ovariectomized women with intact adrenals, the plasma levels were similar, 16 ± 1 ng/dl, 3 ± 1 ng/dl, and 26 ± 4 pg/dl, respectively (P = NS).

In both postmenopausal and ovariectomized women with adrenal insufficiency, the plasma Adione levels were below the limit of the assay or close to the limit of the assay (Fig. 1).

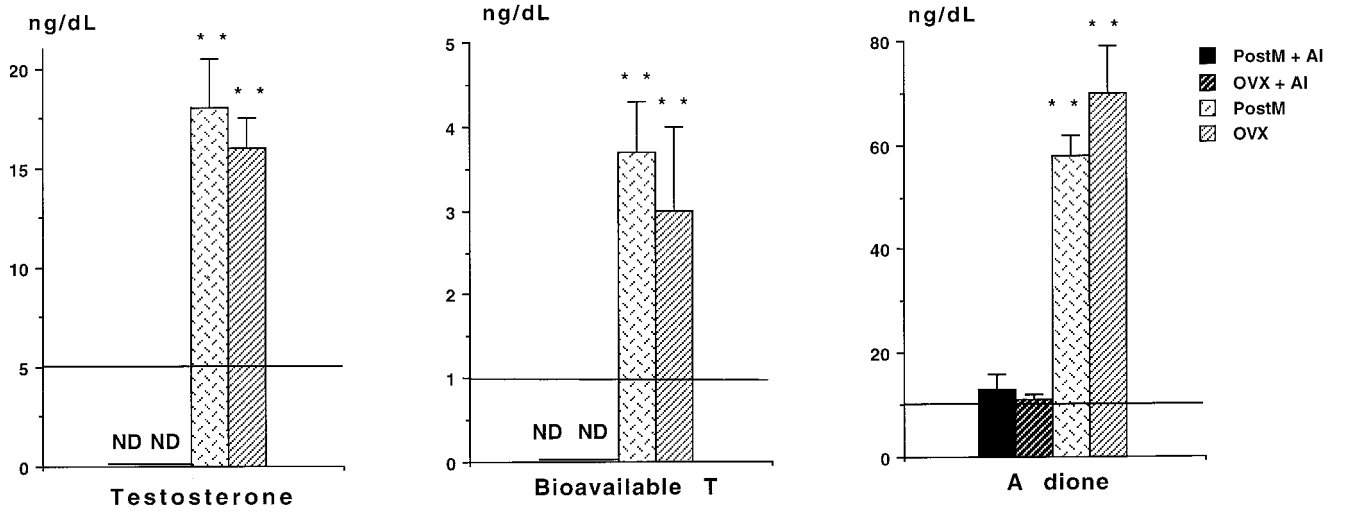

FIG. 1. Plasma T, bioavailable T, and Adione levels in postmenopausal women with adrenal insufficiency (PostM + AI), ovariectomized women with adrenal insufficiency (OVX + AI), postmenopausal (PostM), and ovariectomized (OVX) women with normal adrenal function. The *horizontal line* represents the limit of sensitivity of the assay. *, P = NS between PostM and OVX with AI. **, P = NS between PostM and OVX with normal adrenal function. To convert values for T and bioavailable T to nanomoles per liter, multiply by 0.03467; to convert values for Adione to nanomoles per liter, multiply by 0.0349. ND, Not detectable.

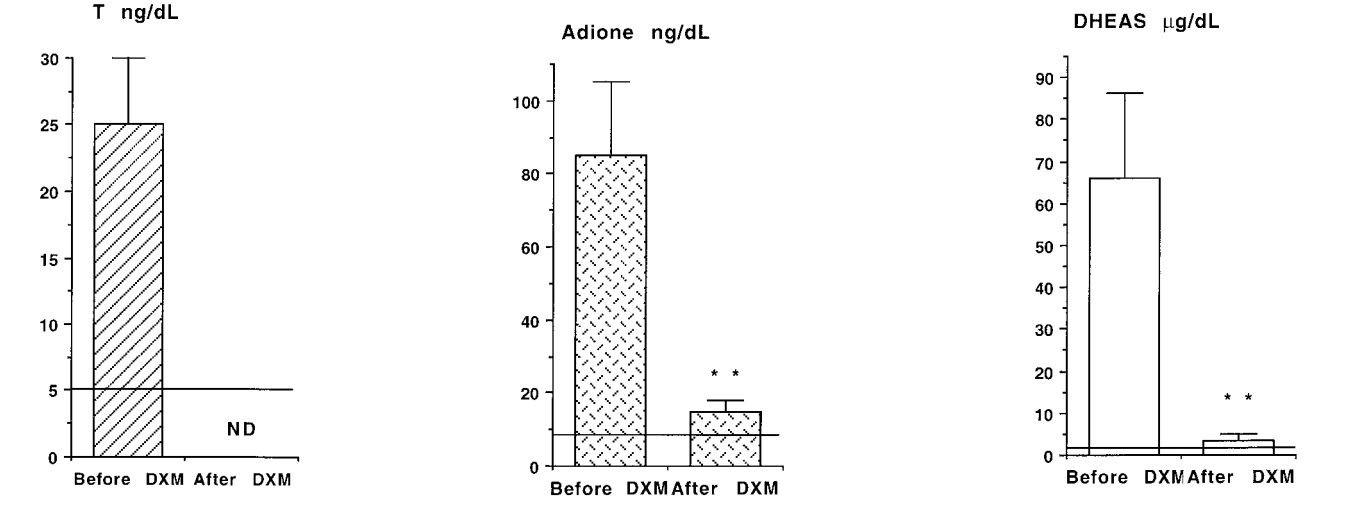

FIG. 2. Plasma T, Adione, and DHEAS levels after DXM administration in postmenopausal women with normal adrenal function. The *horizontal line* represents the limit of sensitivity of the assay. **, $P < 0.001$ between before and after DXM. To convert values for DHEAS to micromoles per liter, multiply by 0.02714. ND, Not detectable.

In postmenopausal and ovariectomized women with intact adrenals (Fig. 1), the plasma Adione levels were similar, 61 ± 4 ng/dl and 70 ± 9 ng/dl, respectively (P = NS).

The plasma DHEAS levels were below the limit of the assay (<2 μg/dl) in women with adrenal insufficiency and low in control women with intact adrenals (58.1 ± 14.9 μg/dl).

The iterative hCG im. injections in the group of postmenopausal women with adrenal insufficiency did not elicit any increase in the plasma T and Adione levels, which remained below the limit of the assay. In the postmenopausal women with intact adrenals, DXM administration decreased dramatically, and in a parallel fashion, T, Adione, and DHEAS levels to levels below or close to the limit of the assays (Fig. 2).

The intraovarian T and Adione levels were less than 0.4 ng/g and 3.3 ± 0.1 ng/g of tissue, respectively, in homogenates of the postmenopausal ovarian tissues, compared with controls (33 ± 8 ng/g and 87 ± 12 ng/g of tissue, respectively).

Immunocytochemical detection of steroidogenic enzymes and gonadotropin receptors in the ovaries

In the eight premenopausal ovarian controls, immunostaining for the four enzymes (P-450 aromatase, P-450 SCC, 3βHSD, and P-450 C17) was detected in the follicles and corpus luteum in more than 20% of the cells (Fig. 3). Aromatase was absent from the 17 postmenopausal ovaries (Tables 2 and 3). In 13 ovarian samples, the three enzymes were absent or in very low amount in less than 1% of the cells (Fig. 3). In three ovaries (patients 10, 16, and 17), one or two enzymes were present in 1.9%, 2.5%, and

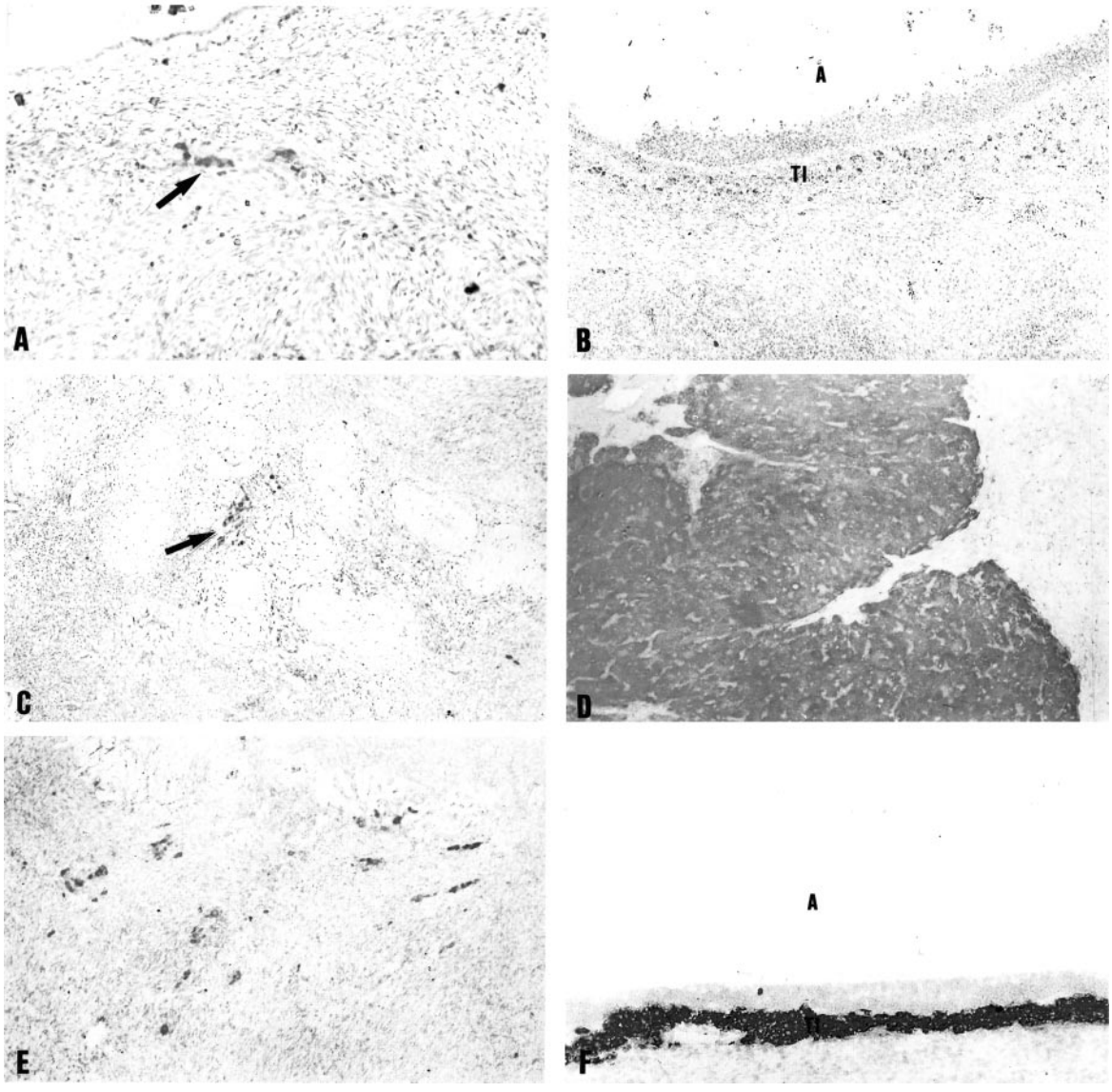

FIG. 3. Immunostaining for P-450 SCC, 3β HSD, and P-450 C17 in postmenopausal ovaries (A, C, E) and control ovaries (B, D, F). Magnification, × 200. Note the almost absence of staining in the postmenopausal ovaries, compared with the intense immunostaining in the controls. TI, Theca interna; A, antrum.

TABLE 2. Steroidogenic enzymes and LH and FSH receptors in frozen ovaries from seven postmenopausal women and four cycling women (controls)

Subjects	Age (yr)	P-450 SCC	3β-HSD	P-450 C17	Aromatase	LHR	FSHR	Number of blocks examined
1	53	—	—	—	—	—	—	6
2	50	—	—	—	—	—	—	1
3	51	—	—	—	—	—	—	3
4	61	—	—	—	—	—	—	3
5	63	—	—	—	—	—	—	3
6	64	IC[a]	IC[a]	IC[a]	—	—	—	3
7	50	—	—	—	—	—	—	3
4 controls	42–50	[b]	[b]	[b]	[b]	[b]	[b]	3/control

—, <1% immunolabeled cells; [a] 9% immunolabeled cells (immunolabeling was restricted to interstitial cells [IC]). [b] >20% immunolabeled cells (follicles or corpus luteum).

3%, respectively, of a few hilar or interstitial cells (Table 3). In only one ovary (patient 6), P-450 SCC, 3β HSD, and P-450 C17 enzymes were detected in 9% of interstitial cells (Table 2). The presence of low amounts of steroidogenic enzymes was observed in ovaries of patients aged 57–64 yr and independent of the duration of menopause.

In the four frozen ovarian controls, LH and FSH receptors were present in more than 20% of the cells. In contrast, in the seven frozen postmenopausal ovaries, including patient 6 with 9% of steroidogenically active cells, FSH and LHRs were completely absent (Table 2 and Fig. 4).

Discussion

The present study demonstrates that the climacteric ovary does not remain a major site of androgen secretion. In postmenopausal women with complete adrenal insufficiency, plasma levels of DHEAS, as expected, but also total T, non-SHBG-bound T, and Adione levels were either below or close to the limit of the assay. Because our assay sensitivities for total and bioavailable T were 5 ng/dl and 1 ng/dl, respectively, these women had extremely low levels of these hormones. The results were similar in ovariectomized women with adrenal insufficiency. In postmenopausal women with intact adrenals, plasma total T represented 50% of the levels observed during reproductive life. This result could not be explained by a decrease in plasma SHBG levels observed after menopause and because of the fall in plasma E2 levels and the increased BMI (20). Indeed, a parallel decrease of the non-SHBG-bound T and plasma Adione levels was observed. The results were similar in ovariectomized women with intact adrenals. Plasma DHEAS levels were also low, but the decrease was variable from one subject to the other. It is now well known that plasma DHEAS levels decrease progressively with age principally in women, independently from menopause (21, 22).

The apparent exclusive adrenal origin of androgens in postmenopausal women is in disagreement with previous studies. Twenty-five years ago it was reported that the climacteric ovary was responsible for 40–50% of plasma T levels and 20–30% of plasma Adione levels (7, 8). These data were supported by the increase of plasma androgen levels after exogenous hCG (8) and the decrease after GnRH agonist or antagonist administration (9, 10, 13). In the present study, in the absence of adrenal steroids and in the presence of intact postmenopausal ovaries, iterative hCG stimulation did not elicit any increase in plasma sex steroid levels. In contrast, in postmenopausal women with intact adrenals, DXM administration suppressed dramatically plasma androgens to levels below or close to the limit of the assays. The decrease of T was parallel to the decrease of plasma Adione and DHEAS levels.

Plasma androgen levels were similar in postmenopausal and oophorectomized women. These results are divergent from previous studies (3, 13, 21). In the study of Laughlin *et al.* (21), plasma T and Adione levels were 40% and 10% lower, respectively, in oophorectomized women than levels in intact postmenopausal women. The possible reason for the discrepancy may be due to differences in clinical characteristics of the women studied. Though there was no difference in ethnicity and BMI, the mean age in our study groups was much younger and the length of hormone replacement therapy withdrawal (at least 3 months) was shorter than in the Rancho Bernardo study (21). A study of 100 women, 1–31 yr after ovariectomy, concluded that, although plasma T levels were lower in recently ovariectomized women, compared with intact postmenopausal women, the difference was minimal 5 yr after surgery (23). In the present study, the minimal duration of menopause or time after surgery was 5 yr. It is also noteworthy that plasma T levels in both postmenopausal and ovariectomized women with intact adrenals (adjusted for age and BMI) were similar to those previously reported in 438 postmenopausal women (21) and in 750 ovariectomized women (4).

The most convincing data, previously reported, were probably the analysis of ovarian and peripheral vein blood showing higher T concentrations in the postmenopausal ovarian vein

TABLE 3. Steroidogenic enzymes in formol-fixed paraffin-embedded ovarian samples from 10 postmenopausal women and 4 cycling controls

Subjects	Age (yr)	P-450 SCC	3β-HSD	P-450 C17	Aromatase
8	55	—	—	—	—
9	60	—	—	—	—
10	58	—	—	HC[a]	—
11	65	—	—	—	—
12	57	—	—	—	—
13	61	—	—	—	—
14	69	—	—	—	—
15	70	—	—	—	—
16	63	IC[a]	—	—	—
17	57	—	HC[a]	HC[a]	—
4 controls	42–50	[b]	[b]	[b]	[b]

—, <1% immunolabeled cells; [a] <3% immunolabeled cells: interstitial (IC) or hilar (HC) cells were stained; [b] >20% immunolabeled cells (follicles or corpus luteum).

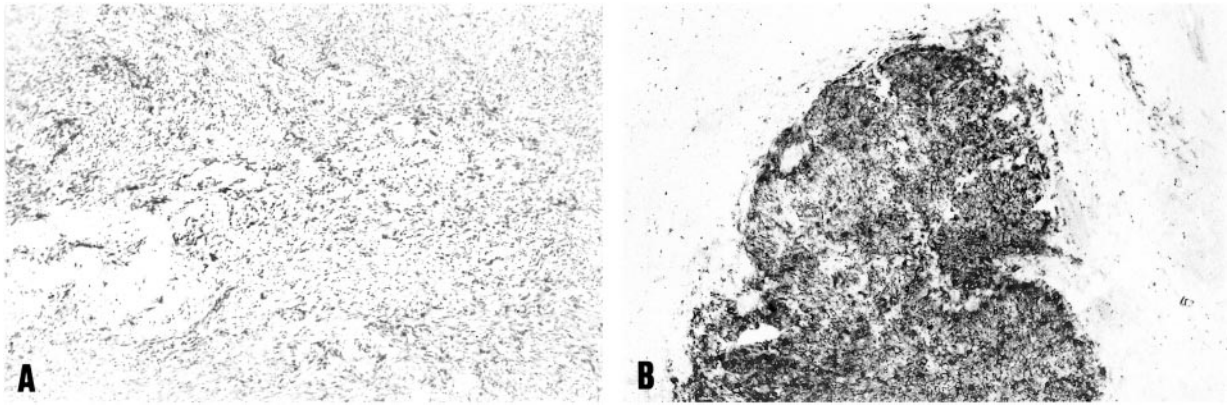

FIG. 4. Immunostaining with the LHR 29 antibody for LH receptors in a postmenopausal ovary (A) and one control (B). Note the intense positive immunostaining in the corpus luteum of the control. Magnification, ×200.

(11–13). However, after menopause, ovaries are atrophic organs, their blood flow is limited, and the ovarian vein is vulnerable. Thus, blood sampling is difficult, and only a small amount of veinous blood is often obtained (24). To avoid these technical drawbacks, we measured T and Adione in postmenopausal ovarian homogenates. Similar to the results of plasma steroid measurements, intraovarian androgens were not detectable in the postmenopausal ovaries, compared with the premenopausal controls.

If the climacteric ovary is a gonadotropin-driven, androgen-producing gland, immunocytochemical studies should recognize the presence of steroidogenic enzymes and gonadotropin receptors. To our knowledge, there have been few reports about the steroidogenesis in the postmenopausal ovary. Inkster and Brodie (25) reported that in postmenopausal ovaries, individual cells and clusters of cells in the stromal compartment of three out seven specimens were found to have an aromatase immunostain reaction. In contrast and in agreement with the present data, Sasano *et al.* (26) reported a total absence of aromatase. The enzyme 3β HSD was found by immunostaining in the cytoplasm of only a few dispersed interstitial cells of five postmenopausal ovaries (27). The expression of the P-450 C17 gene was observed by PCR, with great variations between samples, in only four postmenopausal ovaries (28).

The present study clearly showed that the steroidogenic enzymes, P-450 SCC, 3β HSD, and P-450 C17, were either absent, like the aromatase enzyme, from the majority of postmenopausal ovaries or present in a limited percentage of cells ($<$1%), compared with more than 20% in the premenopausal controls. The loss of steroidogenically active cells was independent of the age of the patients and the duration of menopause. Three of 17 ovaries contained one or two enzymes (P-450 C17 mandatory for androgen biosynthesis was present in two) in less than 3% of the interstitial or hilar cells. Only one ovary expressed the three enzymes in 9% of the interstitial cells. The presence of the three steroidogenic enzymes in only 1 of the 17 ovaries studied would indicate that less than 6% of postmenopausal women would secrete ovarian androgens. The absence of immunostaining in the other cases is in agreement with the clinical data reported here showing that the climacteric ovary is almost constantly incapable of androgen production.

It is currently believed that the postmenopausal ovary is a site of gonadotropin reception and action (6). If the ovary remained gonadotropin responsive, specific gonadotropin receptors must be characterized in the interstitial and hilar cells. Dennefors *et al.* (29) reported that the addition of hCG to ovarian cortical stroma or hilar tissue of postmenopausal ovaries elicited a significant increase in cAMP formation, indicating a preserved gonadotropin responsiveness of postmenopausal ovaries. Binding sites for gonadotropins have been identified by autoradiography in the cortical stroma of the climacteric ovary (30). However, with the same binding assay, Vikko *et al.* (31) did not confirm these results. The present study is the first one using immunocytochemistry, with three monoclonal antibodies recognizing different epitopes of the extracellular domain of the LHR. This method recognized LH and FSH receptors in more than 20% of the cells in the premenopausal ovaries used as controls. In contrast, in the seven frozen ovaries allowing the study of gonadotropin receptors, immunostaining for LH or FSH receptors was not observed in any of them. Thus, even in the presence of a few steroidogenically active cells, the postmenopausal ovary cannot be stimulated by the high plasma gonadotropin levels. This assertion is based only on immunocytochemical studies. *In situ* hybridization also should be used to study receptor and enzyme mRNA distribution. In addition, the absence of LHRs does not exclude that in some postmenopausal women or in pathological conditions, the ovarian androgen production may be maintained under the influence of other stimulating factors such as insulin or IGF (32, 33). The presence of their receptors has been documented in theca cells (34). Further studies are necessary to assess their presence in the climacteric ovary.

According to the present results, it appeared reasonable to anticipate that the adrenal was the almost exclusive source of plasma-circulating androgens in postmenopausal women. The LH/hCG receptors have been found in the zona reticularis by *in situ* hybridization and immunocytochemistry in humans (35). In addition, hCG has been shown to stimulate DHEAS secretion by the human fetal adrenal gland (36). We had the opportunity to study three frozen normal human adrenal glands, with the same monoclonal antibodies for LHRs used for the postmenopausal ovaries. LHRs were present in more than 10% of the cells (data not shown). These preliminary results may explain some of the previous results reported in postmenopausal women with intact adrenal function and showing the plasma androgen-LH dependency.

In conclusion, circulating androgens in postmenopausal women do not originate from the ovary but from the adrenal. This result is consistent with the immunocytochemical study, showing the almost constant absence of steroidogenic enzymes (or in very low amount) and the complete absence of LHRs in the postmenopausal ovary. The climacteric ovary does not retain full capacity for androgen biosynthesis and is not activated by the high levels of circulating LH. This is an important issue because it would be unfortunate to abandon the prophylactic bilateral ovariectomy at the time of hysterectomy in postmenopausal women (21). In addition, the fall in total circulating androgens results from ovarian failure and the age-related decline in adrenal androgen production. The androgen deficiency in women after natural menopause may lead to impaired sexual function and psychological changes affecting their quality of life (1–4). The present study argues for the therapeutic use of androgen together with classical hormone replacement therapy in postmenopausal women.

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