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Mammographic changes in women receiving tibolone therapy

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Objective: To investigate the effects of tibolone therapy for menopausal symptoms on mammographic findings and to identify any association between mammographic changes and the demographic and hormonal characteristics of women receiving tibolone.

Design: A prospective study.

Setting: A university hospital.

Patient(s): Seventy-five women who were in the climacteric or postmenopausal period were recruited, and 25 of them were followed up for 24 months.

Intervention(s): After high-resolution mammographies were performed and blood samples were collected, tibolone (2.5 mg/d) was administered orally to all patients. At the end of the 24-month follow-up period, blood samples were collected again and mammographies were repeated.

Main Outcome Measure(s): Serum levels of LH, FSH, prolactin, estradiol, testosterone, and DHEAS were determined from the collected samples, and mammographies were interpreted.

Result(s): At the end of the 24-month follow-up period, mammographic changes were observed in only two women (8%). Women who had no change in mammography constituted group I (n = 23). Women who had a change constituted group II (n = 2). Although the initial hormone levels were not different, the increase in serum DHEAS in group I was significantly higher than in group II ($z = 2.30$, $P = 0.021$).

Conclusion(s): The frequency of mammographic changes in women receiving tibolone therapy was found to be 8% at the end of the 24-month follow-up. The serum DHEAS level may be an important hormonal marker complementary to mammographic screening for women receiving tibolone therapy. We strongly believe that tibolone is safe in terms of mammographic changes in postmenopausal women. (Fertil Steril® 1998;69:870–5. ©1998 by American Society for Reproductive Medicine.)

Key Words: HRT, tibolone, mammographic changes, breast cancer, DHEAS

Breast cancer is the most common gynecologic cancer among women, especially during the postmenopausal period (1). There is considerable evidence that ovarian hormones have important effects on breast cancer risk. Late menarche and early menopause are associated with a lower risk of developing breast cancer (2, 3). There is still no consensus on the effects of exogenous estrogen, alone or in combination with a progestin, on breast cancer risk in postmenopausal women receiving hormone replacement therapy (HRT) to prevent the mortality and morbidity because of cardiovascular disease and osteoporosis (4–8).

Screening mammography is the only proved method for significantly decreasing the overall mortality from breast cancer (9–11). Clinically significant mammographic findings include satellite lesions, circumscribed masses, microcalcifications, asymmetric densities, and skin changes. Mammography is less sensitive in young women, whose breast tissue is dense, than in older women, who tend to have fatty breasts in which mammography can detect ≥90% of malignancies (12, 13).

The effects of HRT on mammographic findings in postmenopausal women are currently under investigation. Some studies have suggested that mammographic changes in postmenopausal women receiving HRT include in-

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creases in density, multifocal asymmetry, and sizes of cysts and fibroadenomas (14–16). Changes in parenchymal density are especially important because increased density may obscure the mammographic signs of breast cancer. Recently we reported an increase in parenchymal density in 11% of women who were receiving HRT (17). Types of HRT regimens prescribed in these studies consisted of estrogen alone or combined estrogen and progestin in various dosages and durations.

Org OD 14 (7α,17α-17-hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one; tibolone) is a new synthetic steroid designed to combine the favorable effects of estrogens, progestins, and androgens in a single substance. It is structurally related to 19-nortestosterone derivatives such as norethisterone and norethynodrel (18). Tibolone is capable of relieving menopausal symptoms (19) and maintaining skeletal integrity (20, 21) with almost no stimulatory effect on the endometrium (21, 22). This lack of endometrial stimulation minimizes the risk of endometrial cancer and the need for regular gestagen-induced endometrial shedding.

In this prospective study, we investigated the effects of tibolone therapy for menopausal symptoms on mammographic findings and determined whether there were associations between mammographic changes and demographic or hormonal characteristics of women receiving tibolone for HRT.

MATERIALS AND METHODS

Between August 1, 1994, and December 31, 1994, 75 women were recruited for this prospective study; 25 women (33.3%) were followed up for 24 months. Fifty women were not compliant and dropped out of the study. Of the 25 women, 3 applied to our clinic during the climacteric, 19 women had spontaneous menopause, and 3 women had undergone surgical menopause. The mean ($\pm$SD) age of the women was 50.40 $\pm$ 4.73 years, and the mean interval from their last menstrual period was 40.96 $\pm$ 31.94 months (range, 8–128 months).

In obtaining medical histories from the participants, we paid special attention to their smoking habits, lactation periods, existence of any previous breast neoplasm, and any breast neoplasm in their families. Breast tenderness was also recorded in their histories. The heights and weights of the women were measured, and body mass index (BMI) was determined. The mean ($\pm$SD) BMI was 27.7 $\pm$ 3.4 kg/m^2. Institutional Review Board approval was obtained. Detailed explanation about tibolone was given to the women, and they each consented to the study.

The climacteric status of each woman was confirmed both by symptoms and by determination of serum levels of FSH, LH, and estradiol. Women who were $>$35 years old and who had a 1-year history of amenorrhea as well as a high gonadotropin level (FSH of $>$40 mIU/mL, LH of $>$25 mIU/mL) and a low estrogen level (estradiol of $<$40 pg/mL) were classified as menopausal. Because tibolone is a derivative of 19-nortestosterone, we also determined initial serum DHEAS and testosterone and prolactin levels. Serum prolactin, LH, and FSH levels were measured by the double-antibody RIA technique (Diagnostic Products Corporation, Los Angeles, CA). Serum estradiol, testosterone, and DHEAS levels were measured by the Coat-a-Count RIA kit (Diagnostic Products Corporation).

High-resolution mammography was performed before the start of tibolone therapy and was repeated at 6- to 12-month intervals according to the women's complaints, breast examination results, and mammographic findings. After detailed histories and physical, hormonal, and radiologic examinations were completed, 2.5 mg/d of Org OD 14 (tibolone, Livial; Organon, Oss, the Netherlands) was administered continuously to the women. At the end of the 24-month follow-up period, the physical, hormonal, and radiologic examinations were repeated.

All mammograms were obtained with the use of high-resolution film equipment (Mammomat-3; Siemens, Erlangen, Germany) in the bilateral craniocaudal and mediolateral oblique positions and in the lateral position if needed. Breast ultrasonography (Sonoline SI-400, 7.5-MHz linear probe; Siemens) was added to mammography as a complementary method for confirmation of any cyst formation. The initial and the last mammograms were interpreted by three experienced mammographers (C.A., G.E., and A.A.) in the Department of Radiology.

After three mammographers reviewed the mammograms, a consensus was reached as to whether there was a subjective increase in density and whether this was focal, multifocal, or diffuse. Mammograms were also evaluated for the presence of masses, cyst formation, and microcalcifications. A focal increase in density was defined as a single area of increased mammographic density without an overall increase in density. A multifocal increase in density was defined as two or more discrete areas of increased density without an overall increase in density. Diffusely increased density was defined as an overall increase of $\geq$10% in density of the breast. Any suspicious mammographic finding warranted histopathologic verification.

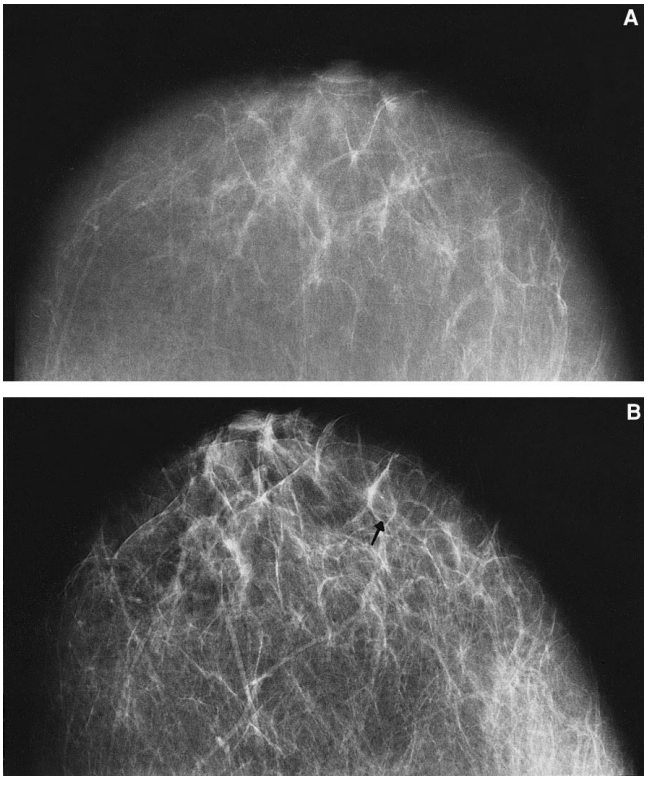
For statistical analysis of the data, Wilcoxon and Mann-Whitney *U* tests were used.

RESULTS

At the end of 24 months, no mammographic changes were observed in 23 women (92%) receiving tibolone therapy. Mammographic changes were observed in 2 women (8%) when their last mammograms were compared with their initial examinations. One of these women had a 10% increase in parenchymal density, and the other had microcalcifications. Women who had no parenchymal changes in

FIGURE 1

The initial (**A**) and the last (**B**) mammograms of the right breast of a patient at the craniocaudal projection. Unlike the initial one, the last one has microcalcifications (*arrow*).



mammography during the study period constituted group I (n = 23), and the women who had changes constituted group II (n = 2).

After 24 months of tibolone therapy, microcalcifications were detected in the upper outer quadrant of the right breast of one woman in group II (Fig. 1). An excisional biopsy was performed. Histopathologic examination revealed dystrophic calcification, ductal cystic dilatation, ductal fibrosis, and mild ductal epithelial proliferation (Fig. 2). The woman decided to discontinue therapy. The other woman in group II showed a 10% density increase between her initial and last mammograms. Histopathologic examination of the dense breast tissue showed fibrocystic changes.

There was no significant difference between groups I and II in terms of age, duration of menopause, BMI, or duration of lactation (Table 1). Two women in group I were heavy smokers, and the mother of another woman in the same group had breast cancer. Three women in group I had surgical menopause. Both women in group II were postmenopausal on entry into the study.

Table 2 shows the means of the initial and last serum determinations of FSH, LH, prolactin, estradiol, DHEAS, and testosterone for the entire series and for women in each group. The differences between the initial and last serum FSH, estradiol, and DHEAS levels of the entire series were found to be significant. After tibolone therapy, the mean (±SD) serum DHEAS level increased from 1,092 ± 522.1 ng/mL to 1,837.2 ± 977.4 ng/mL in the whole group (z = 4.35, P <0.001), whereas mean serum FSH and estradiol levels decreased (z = 2.14, P = 0.032 and z = 2.51, P = 0.012, respectively). When the two groups were analyzed separately in terms of the differences between the initial and last serum hormone levels, a statistically significant increase in serum DHEAS levels (z = 4.20, P <0.001) and a decrease in serum estradiol levels (z = 2.19, P = 0.028) were found in group I.

There was no significant difference between groups I and II when the initial serum hormone levels were compared. However, the difference between the initial and last serum DHEAS level in group I was higher than in group II (z = 2.30, P = 0.021).

DISCUSSION

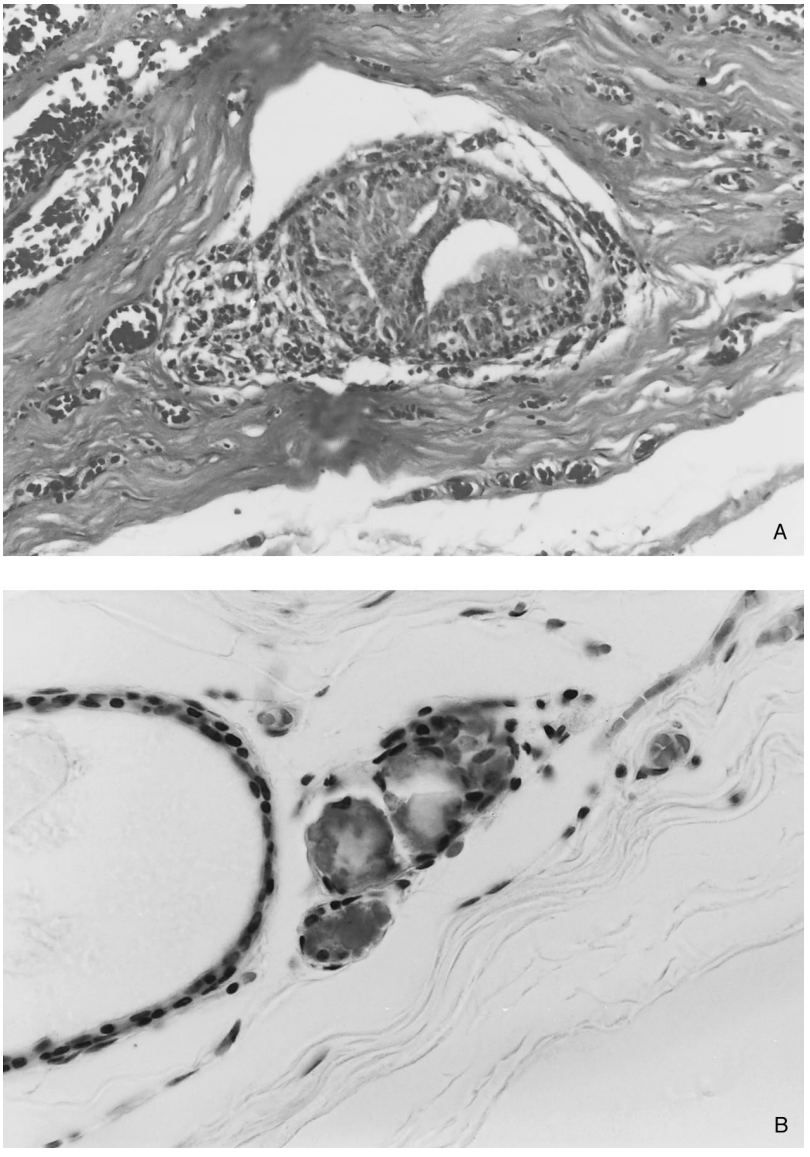
The effects of HRT on breast cancer risk are still being debated, and clinicians are seeking alternatives for estrogen replacement therapy (4–7). Mammography is the most effective screening method for breast cancer detection. Therefore, mammographic changes in women receiving HRT are important. In a discussion of the changes caused by HRT, Wolfe (12, 23, 24) emphasized changes in breast parenchymal density associated with aging and developed a mammographic classification to show an association between the increase in density on mammogram and malignancy. The frequency of encountering such an increase in mammographic density in women taking HRT has been reported to range from 11% to 27% (14–17, 25). In all of these studies, estrogen alone or estrogen and progestin combinations were used for HRT.

It has been reported that the new synthetic steroid tibolone has weak estrogenic, androgenic, and progestagenic activities (18). Tibolone has been used in postmenopausal women as an alternative therapy to estrogen-based HRT. The effect of tibolone on breast cancer risk has not been studied extensively. Mammographic changes also have not been investigated in women taking tibolone.

In this prospective study, 25 women who were receiving tibolone therapy initially had a normal mammogram; at the end of the 24 months, 2 (8%) of these 25 women had an abnormal mammogram. Microcalcifications were detected in one woman, and a denser breast parenchyma was detected in another woman. When taking into consideration an increase in the density of breast parenchyma only, tibolone therapy seems to be superior to estrogen-based HRT. The frequency of increases in mammographic density with estrogen-based HRT has been reported to be higher than that encountered in

FIGURE 2

(**A**) Mild ductal epithelial proliferation (stain, hematoxylin and eosin; original magnification, ×200) and (**B**) focal dystrophic calcifications (stain, hematoxylin and eosin; original magnification, ×400) were detected after excisional biopsy of the lesion shown in Figure 1B.



this study with tibolone (11%–27% versus 4%, respectively) (14–17, 25).

Clinical studies support our hypothesis about the effects of tibolone on breast tissue. When Ginsburg et al. (26) reported their clinical experience with tibolone over 8 years, they emphasized a group of 27 women with benign breast disease and 11 women who had undergone surgery for breast cancer. These women were referred specifically for consideration of nonestrogenic therapy because of a history of breast dysfunction and received tibolone therapy. These investigators did not observe any breast symptoms in any of the 27 women with benign breast disease, and breast symptoms were reported in only 7.5% of their entire series of 301 women (26).

Although our experience was limited, we could not detect any breast discomfort in the 25 women receiving tibolone during the 24-month study period. Recently, O'Brien et al. (27) used tibolone to treat 14 postmenopausal women with advanced or metastatic breast cancer in whom tamoxifen therapy had failed. After 12 weeks of treatment, they noted one patient with a partial response.

TABLE 1

Age, BMI, and duration of menopause and lactation in all 25 women and in women in the two groups separately.

Variable	Whole group (n = 25)	Group I (n = 23)	Group II (n = 2)
Age (y)	50.40 ± 4.73	50.39 ± 4.83	50.50 ± 4.95
BMI (kg/m^2)	27.72 ± 3.41	27.54 ± 3.38	29.82 ± 4.21
Duration of lactation (mo)	13.52 ± 6.57	13.17 ± 6.67	17.50 ± 4.95
Duration of menopause (mo)	40.96 ± 31.94	38.39 ± 26.94	70.50 ± 81.32

Note: All values are means ± SD.

The effects of tibolone on the breast parenchyma and on mammographic findings might be different from the effects of estrogen. There is considerable evidence that estrogen stimulates the proliferation of breast cancer cells (28, 29). Recently, Kloosterboer et al. (30) investigated the effects of norethisterone, 3-ketodesogestrel, gestodene, progesterone, and tibolone on the growth of breast tumor cells in vitro and in vivo. They found, surprisingly, that tibolone was more effective than the others in the 7,12-dimethylbenz(α)anthracene (DMBA) model using the therapeutic approach. Tumor development was delayed and tumor growth was strongly suppressed. The inhibitory effects of tibolone on tumor growth may be attributed to its androgenic activity. Dauvois et al. (31) also showed the inhibitory effect of androgens on DMBA-induced mammary carcinoma in the rat.

In the present study, when women with no change in their mammograms (n = 23) were compared with those women who had a mammographic change (n = 2), we detected a significant difference in the amount of increase in serum DHEAS levels. The increase in group I was significantly higher than the increase in group II, although the initial serum DHEAS levels were not different between the groups.

Zumoff et al. (32) revealed an association between breast cancer and low concentrations of DHEA in premenopausal women. Ebeling and Kolvisto (33) proposed that DHEA had either an estrogenic or an androgenic effect depending on the hormonal milieu. In premenopausal women, DHEA might inhibit the growth of breast cancer cell lines, either directly or via conversion to androstanediol, which has antiestrogenic properties. In postmenopausal women with a low estrogenic milieu, DHEA might act as an estrogen agonist, stimulating tumor growth.

Because tibolone also has weak estrogenic activity, it may maintain the estrogenic milieu in postmenopausal women and thus improve the androgenic effect of DHEA on breast cells. Therefore, women who are found to have no increase in serum DHEAS levels while receiving tibolone may be more susceptible to the estrogenic activity of tibolone and thus to breast cancer.

We previously reported that women who have an increase in parenchymal density on a mammogram have significantly higher serum estradiol levels than women who have no change in density (17). Just as increased serum estradiol levels might be responsible for the increase in density, the antiproliferative effects of tibolone on breast tissue might result from increased levels of serum DHEAS.

In conclusion, the frequency of mammographic changes in women receiving tibolone was found to be 8% at the end of 24 months of follow-up. The serum DHEAS level may be an important hormonal marker complementary to mammographic screening for women receiving tibolone. The association between the increase in serum DHEAS levels and normal mammograms of women receiving tibolone deserves further study.

The strengths of this study include its prospective design, measurement techniques, evaluation of mammograms by three experienced radiologists, and demographic and hormonal information on the patients. On the other hand, limitations include the absence of a randomized control group and the small number of women taking tibolone. Nevertheless, we strongly believe that tibolone is safe in terms of mammographic changes in postmenopausal women.

TABLE 2

Initial and last hormone levels in all 25 women and in women in the two groups separately.

	Whole group (n = 25)		Group I (n = 23)		Group II (n = 2)	
Hormone	Initial	Last	Initial	Last	Initial	Last
FSH (mIU/mL)	65.46 ± 33.24	51.84 ± 20.37	65.69 ± 34.36	52.82 ± 20.91	62.85 ± 22.84	40.6 ± 7.91
LH (mIU/mL)	41.89 ± 13.53	36.25 ± 14.67	41.77 ± 14.10	36.71 ± 15.23	43.2 ± 3.96	30.95 ± 1.34
Estradiol (pg/mL)	27.76 ± 19.64	15.10 ± 11.67	27.43 ± 19.94	15.93 ± 11.69	31.5 ± 21.92	5.55 ± 7.71
Prolactin (ng/mL)	8.01 ± 5.50	7.03 ± 5.44	7.18 ± 2.92	7.09 ± 5.68	17.48 ± 18.58	6.36 ± 0.51
DHEAS (ng/mL)	1,092 ± 522.1	1,837.2 ± 977.4	1,101.3 ± 515.9	1,908.7 ± 969.4	985 ± 813.2	1,014.5 ± 884.6
Testosterone (ng/mL)	0.32 ± 0.26	0.39 ± 0.25	0.33 ± 0.27	0.41 ± 0.25	0.25 ± 0.06	0.15 ± 0.07

Note: All values are means ± SD.

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