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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

A Clinician's Response to the Epidemiological Data Linking Post-Menopausal Estrogen-Progestin Therapy with an Increased Risk of Breast Cancer

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INTRODUCTION

In the January 26, 2000, issue of *JAMA*, Schairer and colleagues from the National Cancer Institute (NCI) reported the results of a retrospective cohort study, comparing the risks of breast cancer associated with postmenopausal hormone regimens of estrogen alone or a combination of estrogen and progestin.[1] The follow-up data were derived from the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program. The authors concluded that current and recent users (within the four years prior to diagnosis of breast cancer) of an estrogen-progestin regimen increases the risk of breast cancer more than estrogen alone, relative risk of 1.4 (1.1-1.8) and 1.2 (1.0-1.4), respectively. These relative risks were interpreted in the press releases as indicating a two-fold difference.

As in other studies,[2] this report found an increased risk associated with estrogen alone, only in long-term users who were lean. A favorite explanation is to suggest that this is because the effect of estrogen is no greater than the effect associated with increased estrogen production in overweight women. The increases in risk associated with estrogen only treatment were observed only in women with a BMI of 24.4 or less, achieving statistical significance only after six years of use, RR=1.5 (CI=1.2-2.0). Similarly, an increase with duration of use in the estrogen-progestin group was significant only in the lean women.

In the February 16, 2000, issue of the *Journal of the National Cancer Institute*, Ross and colleagues from the University of Southern California reported the results of a population-based case-control study that also indicated a greater increased risk of breast cancer associated with the use of estrogen and progestin compared with estrogen alone.[3] They further concluded that a sequential combination of estrogen and progestin was associated with a greater risk of breast cancer than the risk associated with a daily continuous regimen of estrogen and progestin. The findings that deserve highlighting, in my view, were as follows:

The analysis of estrogen alone regimens indicated no statistically significant increased risk of beast cancer, even with

FROM THE EDITOR

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CONTROVERSY is the appropriate appellation. BREAST CANCER is the problem. ANXIETY is the result. Dr. Leon Speroff, the first editor of *Menopausal Medicine* and an editorial board member, addresses the recent publications on the epidemiology of breast cancer and the use of Estrogen-Progestin Replacement Therapy. There is no simple answer, but Dr. Speroff presents his usual insightful analysis of the literature for your consideration.

Dr. Jennifer A. Harvey describes the impact of estrogen-progestin replacement on mammographic imaging. Routine mammography is felt to be one of the reasons for the early detection of breast cancers. Her report of a 37% incidence of further diagnostic studies in women using HRT should be contrasted with an increased incidence of anxiety in women who were recalled for further studies [Gilbert FJ, et al. Breast screening: the psychological sequelae of false-positive recall in women with and without a family history of breast cancer. *Eur J Cancer.* 1998:34;2010-4].

Dr. Alessandra Graziottin returns with her essay on Loss of Libido. The treatment of reduced libido is dependent on an appropriate diagnosis and assessment of the various factor(s) that make up female sexuality. Hormonal therapy is only one aspect of treatment for this common problem.

Menopausal Medicine

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increasing duration of use up to more than 15 years (Odds ratio = 1.06; CI = 0.97-1.15). In contrast to other reports (such as the Nurses' Health Study), no difference was found comparing current users with past users. When analyzed by stage of disease, combined estrogen-progestin regimens were associated with a barely significant increase in localized disease and no significant increase in in situ or advanced disease; sequential estrogen-progestin regimens with a significant increase in localized disease and no significant increase in in situ or advanced disease; and daily estrogen-progestin regimens with no significant increase in any of the categories. This variation and the strength of the associations (relative risks that range from 0.98 to 1.44) do not provide evidence of a major effect.

The difference between sequential and daily estrogen-progestin regimens was not statistically significant, but the authors were obviously unencumbered by this fact in their emphasis upon a difference between the regimens. The increased relative risks associated with sequential and daily estrogen-progestin regimens for more than 10 years were based on 27 cases/14 controls and 13 cases/20 controls, respectively; hardly the robust numbers claimed by the authors in their introduction.

STRENGTH OF THE CONCLUSIONS

These recent publications join others[2,4,5] in reporting a relative risk that at best represents a weak association or that is the result of confounding factors that are difficult to overcome in observational studies. In the study from the National Cancer Institute, the authors expressed observed and predicted increases in relative risk for estrogen only and estrogen-progestin for each year of use in a figure illustrating a "linear excess risk" model, which indeed demonstrates rising lines, a significant trend with increasing duration of use. However, each point in both the estrogen only and the estrogen-progestin graphs is accompanied by a portrayal of the confidence intervals that all, with one exception in each graph, cross 1.0 and are not statistically significant (eight of 10 points were not statistically significant).

The accompanying editorial, written by three of the investigators with the Nurses' Health Study, advanced a point of view that, in my view, is more definitive than justified. The editorial informed us that a preliminary updated report from the Nurses' Health Study indicated that the risk of breast cancer is increased more with combined use than by estrogen alone.[6] In the preliminary update from the Nurses' Health Study, the cumulative risk for 10 years of estrogen use was 1.11, and for estrogen-progestin 1.58, with the annual increases for each treatment being significantly different.[6] In the last published full report from the Nurses' Health Study, the authors wrote that the risks associated with estrogen alone and with combined estrogen and progestin did not differ significantly from each other.[4] The update report, in abstract form, does not provide the data to allow an evaluation of confidence intervals.

The emphasis and interpretation of the current reports examining the effect of estrogen and progestin could be of a totally different nature. The numbers indicate a lesser, and in many instances no significant increased risk, with estrogen therapy, even of long duration, a conclusion based on more cases when compared with the number of cases in estrogen-progestin users. For example, in the current report from the NCI, 38% of the cases were users of estrogen alone, and only 4% were estrogen-progestin users.[1] If one placed the emphasis where the greater numbers are, the message would be a reassuring one.

A review of the previous epidemiologic reports examining the risk of breast cancer associated with postmenopausal estrogen-progestin therapy finds that there are three studies with statistically significant increased risks, ranging from a relative risk of 1.41 to 1.7,[2,4,5] and there are 10 reports with relative risks that are not statistically significant.[5,7-15] Thus, the available epidemiologic evidence on the impact of combined estrogen-progestin treatment on the risk of breast cancer indicates a mixed story, not a uniform and consistent result as implied in the *JAMA* editorial.

BREAST CANCER SURVIVAL IN POSTMENOPAUSAL HORMONE USERS

Most of the studies that have examined the breast cancer mortality rates of women who had used postmenopausal hormone therapy have documented improved survival rates.[16-25] Even studies that detect an increased risk of breast cancer in hormone users indicate a paradoxical better outcome. This undoubtedly partly reflects earlier diagnosis in users because the greater survival rate in cur-

rent users is associated with a lower frequency of late stage disease.[14,17,21,24, 26-29] In the reanalysis of the worldwide data, "among current or recent users of hormone replacement therapy, the excess risk of breast cancer was confined to localized disease."[14] Increased utilization of mammography by hormone users is a well-recognized phenomenon. A greater frequency of mammography and breast examinations among hormone users introduces detection/surveillance bias into all observational studies

There is also evidence to suggest that estrogen users develop smaller, better-differentiated (lower grade) tumors, and that surveillance/detection bias is not the only explanation for better survival.[27,29,31-34] These biologic differences imply that hormone treatment promotes the growth of a malignant locus already in place, and it presents clinically with a more favorable biology. This conclusion is consistent with the fact that virtually all the positive studies find that any increase in risk disappears within five years of discontinuing hormone therapy, and tumors occur at an earlier stage and a younger age in women using hormone therapy. It should be noted that one study reported high S-phase fractions among estrogen receptor positive breast cancers in women who were hormone users, and it is not apparent why this study differs from the others.[35]

Lower grade tumors are present even when there is no difference in the prevalence of mammography comparing hormone users and nonusers, or when the data are adjusted for the method of detection.[23,25,34] The favorable phenotype characteristics in hormone users have also been documented to be independent of tumor size.[29,31,32] In the Breast Cancer Detection Project, current hormone use was associated with a 40% to 60% reduction in breast cancer mortality for 12 years after diagnosis.[23] This effect remained after correcting for cases detected at the first screening visit and when in situ data were excluded, indicating that the results were not due to detection/surveillance bias. In this report, the protection against breast cancer mortality associated with hormone use could not be attributed to tumor size, age at diagnosis, BMI, tumor histology, or node status. Thus, an important effect is on grade of disease, tumor differentiation, and aneuploidy. An excess of grade I tumors has been documented equally in users of estrogen alone and in users of combined estrogen and progestin.[36] These observations support an effect of hormone therapy on pre-existing tumors.

THE CELLULAR RESPONSE TO PROGESTINS

Those who promote the idea that exposure to a combination of estrogen and progestin is associated with a greater risk of breast cancer draw heavily on the observations that indicate that fluid secretion, mitotic activity, epithelial proliferation, and DNA production of nonglandular tissue and glandular epithelium peak during the luteal phase.[37-43] Studies using tissue from reduction mammoplasties or from breast tissue near a benign or malignant lesion have demonstrated a peak in mitotic activity during the luteal phase.[38, 44, 45] Using fine needle biopsy tissue, an immunocytochemical marker of proliferation was higher in the luteal phase than in the proliferative phase.[46] And in this study there was a direct correlation with serum progesterone levels.

These results indicate that progesterone supports cyclical proliferation in the breast during the normal menstrual cycle and during pregnancy. Therefore, it has been generally accepted that progesterone inhibits the growth of endometrial epithelium during the menstrual cycle, but stimulates growth of the mammary epithelium. There are those who believe this estrogen-progesterone cycle of proliferation accumulates genetic errors that eventually lead to breast cancer.[47]

Recent studies, however, suggest that this initial impression may not be accurate, and that the breast and endometrium are more similar than previously believed. Human breast tissue specimens removed after the patients were treated with estradiol and progesterone indicated that progesterone inhibits in vivo estradiol-induced proliferation.[48] Normal human breast tissue implanted into mice was stimulated by estrogen but NOT progesterone, either alone or after estrogen priming.[49] An increase in DNA synthesis during the luteal phase is correlated with an increase in epithelial mitoses, that peak toward the end of the luteal phase, followed by apoptosis. Women who ultimately develop breast cancer do not have different blood levels of progesterone.[50]

There is growing evidence that progesterone exerts an effect on human breast epithelial proliferation similar to its effect on the endometrium.[48,49,51,52] The key to understanding this effect is appreciating the importance of duration of exposure. Human breast tissue exposed to a combination of estrogen and progestin for 14 days resulted in a decrease in epithelial proliferation.[52] In the postmenopausal monkey, treatment with a combination of conjugated estrogens plus medroxyprogesterone acetate induced a proliferative response in breast epithelium, greater than that with estrogen alone.[53] However with time, combined treatment led to a decrease in the number of estrogen and progesterone receptor positive cells. With human breast cancer cells, progestins inhibit growth and stimulate differentiation.[54] In a study of postmenopausal women who underwent biopsies for malignant or benign breast disease, no significant differences were observed in epithelial proliferation rates in those women receiving either estrogen alone or combined estrogen and progestin compared with women not on hormones.[55] Although the progesterone receptor content was higher in hormone-treated women, there was no difference comparing the levels associated with estrogen alone with those exposed to estrogen and progestin. In a cohort of 1,150 premenopausal French women with benign breast disease, exposure to 19-nortestosterone agents was associated with a 52% (RR = 0.48; CI 0.25-0.90) reduced risk of breast cancer.[56]

Studies of the T47D breast cancer cell line indicate that inhibition of growth by progesterone is due to the ability of progesterone to induce differentiation and normal gene expression.[54] In breast cancer cells, in vitro, progesterone and progestins produce a transient increase in cell cycle progression, associated with a short-lived induction of genes associated with cell growth.[57] This is an effect on cells already in the growth cycle, not new initiation of growth. In addition, progesterone may inhibit expression of genes involved in suppressing growth. Specifically, progestins decrease the expression of tumor suppressor protein p53, and loss of this response may be involved in unregulated proliferation.[58] Because progesterone inhibits the growth of T47D cells but increases the stimulating growth factors, this was confusing until it was appreciated that the increase in stimulating factors is transient and followed by inhibition.[59]

These studies do not provide a physiological foundation that incriminates prog-

estins in the pathogenesis of breast cancer. Those who implicate progestins have given great weight to the observation that proliferation and mitotic activity peak in the luteal phase. The studies reviewed above, however, indicate that prolonged exposure to a constant level of progestin (unlike pregnancy or a menstrual cycle) provides an inhibiting influence, a possible advantage for the postmenopausal regimen of the daily, continuous administration of estrogen-progestin.

CONCLUSION

Is there a slight risk of breast cancer (in lean women) with long exposure to estrogen-progestin or is this a problem of an imprecise conclusion, in a range easily affected by biases and small numbers? I don't know the right answer, but, in my view, the relative risks are not high enough or precise enough to allow a definitive clinical conclusion. Additional case-control and cohort studies will only confirm the variability and inconsistency of the findings thus far. It is unlikely that the publication of the full update from the Nurses' Health Study, anticipated in the coming months, will change the numbers and thoughts I have recorded here. The answer must await the results of randomized clinical trials.

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The Mammogram in Menopause: How Hormones Influence Imaging

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INTRODUCTION

Estrogen for hormone replacement therapy (HRT) is one of the most commonly prescribed medications in the United States. While HRT has well known beneficial effects, estrogen and progesterone also exert well-defined effects on mammary tissue. HRT induces breast proliferation resulting in a number of mammographic changes, which can decrease mammographic specificity and sensitivity. Because of increased breast proliferation, women who demonstrate HRT-induced mammographic changes may be at increased risk for developing breast cancer.

EFFECTS OF ENDOGENOUS HORMONES ON THE BREASTS

In girls undergoing early puberty, estrogen stimulates proliferation of the entire ductal system and causes an increase in ductal branching. Later in the pubertal process, when cyclic ovulation is established, luteal phase progesterone levels stimulate alveolar cell proliferation. Without progesterone, lobulo-alveolar proliferation does not occur. In response to the cyclic increases in estradiol during the menstrual cycle, the terminal end buds of the ducts proliferate more rapidly, with sparing of the more proximal regions. Remarkably, the changing hormone concentrations during the menstrual cycle produce exceedingly rapid increases and declines in rates of cell proliferation. This rapid responsiveness to hormonal fluctuations can be demonstrated mammographically, since breast tissue is less radiographically dense during the follicular phase than the luteal phase of the menstrual cycle.[1]

With the reduction of estrogen and

progesterone levels after menopause, the cyclic proliferative process involving ductal and alveolar tissue becomes quiescent. Lobular tissue regresses while the more proximal portions of the ductal system remain. Hormone responsive glandular elements persist in the absence of continued ovarian estrogen and progesterone secretion. Consequently, re-growth of glandular tissue occurs upon re-exposure to estrogen, even if the breast has been deprived of hormonal stimulation for a prolonged period of time. The most striking evidence of this fact is the gynecomastia that occurs in men treated with DES for prostate cancer who have not been exposed to significant amounts of estrogen since birth. Thus, while the breast becomes quiescent with menopause, it remains responsive to estrogen stimulation.

NORMAL BREAST CHANGES WITH MENOPAUSE

In response to the decreased estrogen and progesterone levels associated with menopause, the mammographic appearance of the breasts becomes increasingly radiolucent. For example, 76% of women age 75 to 79 have fatty replaced breasts on mammography compared to 38% of women age 25 to 29.[2] Conversely, 39% of women age 25 to 29 have dense fibroglandular tissue on mammography compared to only 6% of women age 75 to 79.[2] Mammography is more sensitive for detecting breast cancers in older women than younger women[3] probably because of the increasing incidence of fatty replacement of the breasts with advancing age.

Benign breast masses, such as fibroadenomas and cysts, become much less common after menopause. Fibroadenomas are the most common breast mass in women below the age of 35 years, when estrogen levels are highest. They also tend to grow rapidly in states associated with high hormone levels such as pregnancy and puberty. But in postmenopausal women, fibroadenomas degenerate due to lack of estrogen exposure resulting in a decrease in size, and they often calcify. Likewise, cysts are very common in middle-aged women, but are very uncommon after menopause. Thus, new benign breast masses are uncommon in postmenopausal women, such that interval development of a mass in this age group is suspicious for breast cancer and biopsy is often recommended.

HRT-INDUCED MAMMOGRAPHIC CHANGES

HRT slows normal breast involution and causes an increase in mammographic density. Benign breast masses, including fibroadenomas and cysts, become more common.

Breast density increases in 17% to 73% of women undergoing HRT.[4-7] In some cases, the mammographic breast density may increase dramatically with the breast tissue becoming more homogeneous (Figure 1), which may also result in an overall enlargement of the breasts.

Two studies have characterized the mammographic changes associated with HRT. In one retrospective study,[4] mammography demonstrated a diffuse increase in density in 14% and multifocal changes in 4% of women on various HRT types. A small prospective study[5] reported similar results with a focal increase in mammographic density in 13%, multifocal in 13%, and diffuse in 3% of women on estrogen with varied amounts of progesterone. Thus, HRT use may result in a diffuse, multifocal, or focal increase in breast density.

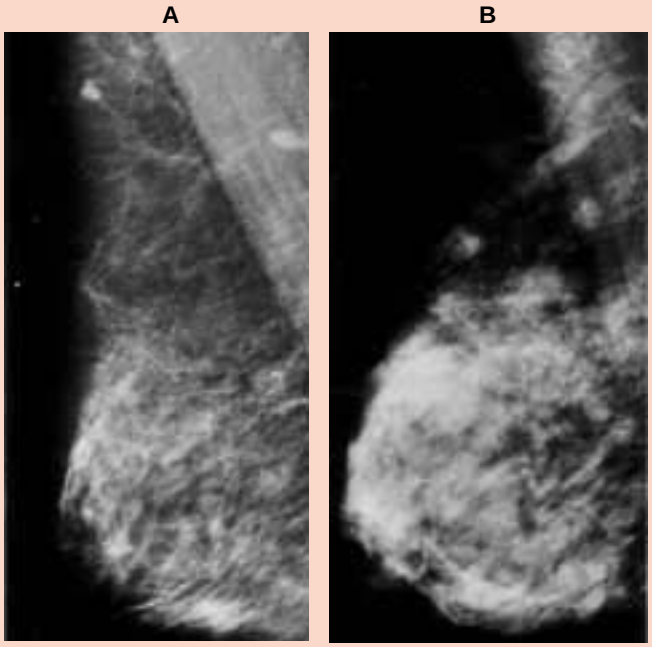
Mammographic changes vary with different HRT regimens. Estrogen combined with progestins has the strongest association with increase in mammographic density, especially for women using continuous combined therapy. In one study, 27% of women undergoing continuous combined therapy had an increase in density compared to 10% of those using cyclic therapy, and only 5% of women using estradiol alone.[6] Another study evaluating only women using continuous combined HRT showed an increase in density in 73% of women,[7] whereas other studies evaluating various types of HRT (with and without progesterone) show an increase in density in only 17% to 27% of women .[4-6] Thus, estradiol alone appears to have the smallest number of women with mammographic changes compared to estrogen combined with progestins. HRT-induced increase in breast density may also be associated with breast pain. In one study, seven of nine women (78%) with a mammographic increase in breast density also developed moderate or severe breast pain.[5] In contrast, 16% of women using HRT without a subsequent increase in density developed mild breast pain.

Fibroadenomas fluctuate in response to hormones. While fibroadenomas usually decrease in size and calcify after menopause, HRT can stimulate growth. These present as an enlarging solid, lobulated or circumscribed mass and biopsy is usually indicated. We have found these to be particularly common in peri-menopausal and recently menopausal women using HRT, and very uncommon in older menopausal women.

Cysts are reported to occur in 6% of postmenopausal women using HRT.[4] In a recent review at our institution,[8] 7% of postmenopausal women undergoing HRT were evaluated for new or enlarging masses that were subsequently shown to represent breast cysts, compared to 1% of postmenopausal women not undergoing HRT.

Cysts present as new or enlarging circumscribed, round or oval, single or multiple masses on mammography. Ultrasound is diagnostic if all criteria for a

Figure 1



Mammographic changes associated with HRT. Right mediolateral oblique (MLO) views before (A) and one year after (B) starting HRT. The breast is larger and the tissue is much denser.

simple cyst are fulfilled. Cyst aspiration may be necessary to exclude malignancy if all sonographic criteria for a simple cyst are not met, or to relieve pain.

HRT-INDUCED MAMMOGRAPHIC CHANGES INFLUENCE OUTCOME

The increase in mammographic density and incidence of benign masses resulting from HRT use can influence the specificity, sensitivity, and cost of mammography. In addition, women who demonstrate an HRT-induced increase in breast density may have an increased risk of breast cancer.

Specificity is reported to decrease 1% to 4% for current users of HRT compared to former and never users of HRT.[9,10] This decrease is likely secondary to additional imaging evaluation or biopsy of HRT-induced changes such as focal asymmetric densities, cysts, and enlarging fibroadenomas.

Although an increase in mammographic density due to HRT does not cause concern if diffuse and symmetric, focal mammographic changes often prompt additional evaluation and subsequent biopsy. Both developing focal asymmetric densities and new or enlarging circumscribed masses are of low, but real, mammographic suspicion. A developing focal asymmetric density is an early sign of breast cancer with a positive predictive value for cancer of 9%.[11] A circumscribed mass on a baseline mammogram has a positive predictive rate of only 1.2% for malignancy, such that short-term follow-up is an appropriate alternative to biopsy.[12] However, if a circumscribed mass is new or enlarging compared to a previous mammogram, biopsy should be considered rather than mammographic follow-up since a significant interval change has already occurred.[12] HRT has been found to induce both of these low suspicion mammographic findings.[4,5] Thus, HRT-induced mammographic changes may prompt recommendations for diagnostic mammography or ultrasound, and biopsy may subsequently be recommended.

Evaluation of both focal densities and new or enlarging masses therefore increases utilization of breast imaging studies for women undergoing HRT. In a recent review at our institution, diagnostic mammograms were performed 37% more often and sonograms 85% more often for postmenopausal women undergoing HRT compared to postmenopausal women who were not undergoing HRT.[8] Cyst aspirations were 10 times more common for postmenopausal women using HRT compared with those who were not using HRT.[8]

While more evaluations are performed for HRT-induced lesions, biopsy rates were similar (2%) for both postmenopausal women undergoing and not undergoing HRT.[8] However, we often use ultrasound or short-term HRT cessation to evaluate probable HRT-induced lesions whereas other practices may recommend biopsy. Therefore, specificity of mammography for women using HRT may vary by practice and if defined using screening recall rates or biopsy rates.

Sensitivity of mammography has been reported as 7% to 15% lower for women using HRT compared to postmenopausal women not using HRT.[3,9] In contrast, a Swedish study has shown no change in sensitivity with HRT use[10] although a high percentage of women in this study defined as undergoing HRT were using only vaginal estrogen, which would not be expected to have a mammographic effect except at high doses.

Two primary explanations for a decrease in sensitivity due to HRT use are plausible. Because HRT slows involution and causes breast proliferation, cancers may be less visible due to the increased mammographic density. In addition, new focal asymmetric densities or masses may be assumed secondary to HRT use and not evaluated. While concern exists that HRT use may decrease mammographic sensitivity, no significant differences in cancer stage have been found between women undergoing and not undergoing HRT.[13] Thus, a small decrease in sensitivity may not be clinically important due to as yet undefined causes such as higher screening rates and shorter screening intervals in women undergoing HRT.

Cost of breast imaging would be expected to be higher for women using HRT due to the increased utilization of breast imaging to evaluate HRT-induced mammographic changes. However, in a recent review at our institution, the overall cost of breast imaging for women using HRT was only $2 more per woman per year ($89) compared to postmenopausal women not using HRT ($87), and was not statistically significant.[8] This was due to the relatively small increase in screening recall rate and low cost of additional imaging studies averaged over the entire screening population.

Breast cancer risk appears to be slightly increased with HRT use, although it is currently not possible to predict which women using HRT are at increased risk. Without considering HRT use, studies using quantitative methods of assessing mammographic breast density have shown an increased risk of breast cancer of four to seven times for women with mammographically dense tissue compared to women with fatty-replaced breasts.[14,15] High-risk histology, such as atypical hyperplasia and lobular carcinoma in-situ, is more commonly seen in women with high density mammograms,[14] supporting the hypothesis that these women are associated with an increase in breast cancer risk.

Since mammographically dense breasts increase breast cancer risk in general, women who have an increase in mammographic density in response to HRT may be at higher risk for developing breast cancer than those women who do not have a change develop. The Women's Health Initiative is currently studying this possibility in a prospective fashion (personal communication). If this theory is correct, alternative treatment for menopausal symptoms such as half-dose HRT or use of a selective estrogen receptor modulator (SERM) such as raloxifene may be indicated for women who develop HRT-induced increase in mammographic density.

MAMMOGRAPHIC DENSITY CAN BE INFLUENCED

While most risk factors for breast cancer cannot be influenced significantly, breast density has the potential to be changed. Evidence of this fact is that while mammographic sensitivity and specificity are lower for current HRT users, former users have the same sensitivity and specificity as women who have never used HRT.[9] This implies that the mammographic changes that influence sensitivity and specificity are reversible.

Short-term HRT cessation can be useful for evaluating mammographic changes that may be HRT-induced. As a routine practice at our institution, we have attempted to reverse focal mammographic changes that may be hormone-induced by discontinuing HRT for two weeks and repeating the mammogram. We have retrospectively reviewed 48 women during a two-year period who developed focal

asymmetric densities or small circumscribed masses that prompted evaluation.[16] These women underwent hormone cessation for two weeks and returned for a repeat mammogram of the breast of concern. For 74% of these women, the abnormality was either decreased in size or had resolved (Figure 2). Of the remaining 12 women whose abnormalities did not change with HRT cessation, four were found to have small benign cysts on ultrasound. Core-needle biopsy was recommended for the remaining eight patients, and one patient had cancer. This resulted in a positive predictive value for biopsy recommendation of 12%. Had hormone cessation not been performed as an initial alternative to immediate biopsy, the positive predictive value would have been only 2% (one cancer in 48 women).

The concern with using HRT cessation as a diagnostic tool is that cancers may also spontaneously regress when estrogen is withdrawn. Although no cancers have been found in follow-up of the above women, we have subsequently had one case in which a patient who underwent hormone cessation with an interval decrease in lesion size after two weeks of HRT cessation was found to have a cancer on her six-month follow-up mammogram. Because of this, we are now using ultrasound more frequently to evaluate developing focal asymmetric densities that may be HRT related. If only fibroglandular tissue is seen indicating that the density is likely secondary to HRT-induced hyperplasia, a follow-up mammogram is performed in six months rather than biopsy. If a mass is localized on ultrasound, then biopsy is recommended.

SERMs should decrease mammographic breast density due to the antiestrogen effect on the breast. A recent study showed a decrease in breast density in the contralateral breast of 60% of women using tamoxifen for treatment of breast cancer, compared to 36% of women undergoing other treatment for breast cancer, and 10% of healthy age-matched women.[17] Tamoxifen use has also been reported to decrease the size and number of breast cysts in two patients.[18]

We have recently begun a prospective randomized clinical trial of 4hydroxytamoxifen (4OHT), which is the most active metabolite of tamoxifen, in a gel form to be applied once daily for 28 days to the breasts of postmenopausal women using HRT with heterogeneously or homogeneously dense breast tissue. A repeat mammogram will be performed at the conclusion of the study. The hypothesized outcome is that the local antiestrogenic effect of the 4OHT upon the breasts will result in a decrease in mammographic density. Should the product prove to be effective, subsequent studies would be performed to evaluate its use for treatment of mastodynia due to breast cysts, decreasing breast density prior to mammography in order to improve sensitivity, and ultimately for breast cancer prevention.

Raloxifene is another SERM that has recently been approved by the Food and Drug Administration for treatment of osteoporosis. Like tamoxifen, raloxifene is an antiestrogen in the breast and has likewise been reported to decrease breast cancer incidence.[19] Thus, raloxifene use would likely result in a decrease in breast density, although no reports have been published to date. Raloxifene differs from tamoxifen as it lacks the estrogenic stimulation upon the uterus that tamoxifen exhibits.

Both tamoxifen and raloxifene decrease breast cancer risk in the short-term. Tamoxifen is associated with a corresponding decrease in breast density. Estrogen, on the other hand, appears to be associated with a small increase in breast cancer risk and can increase mammographic breast density. These findings support the hypothesis that mammographic density is a good indicator of breast cancer risk.

Figure 2

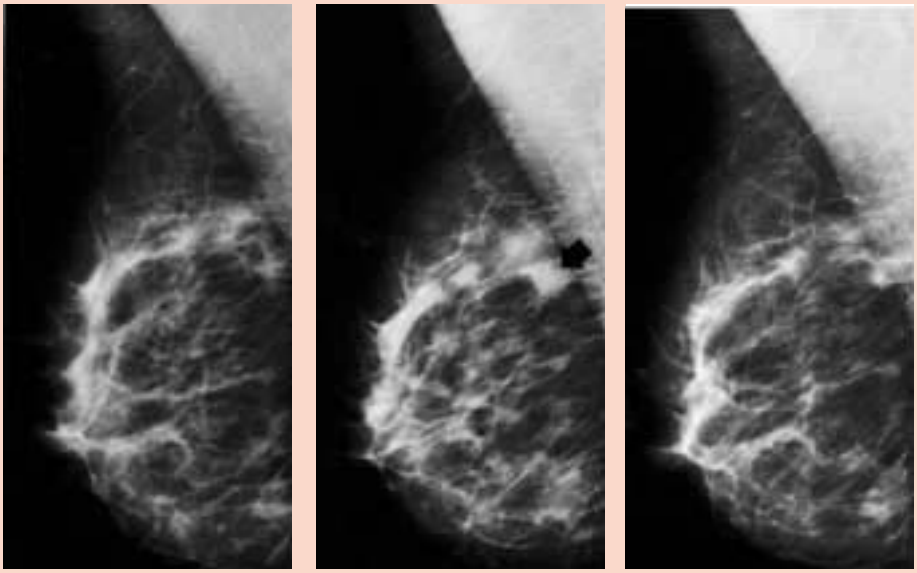


Figure 2. Mammographic response to HRT cessation. Left MLO views before (A) and two years after starting HRT (B) show interval development of a focal asymmetric density (arrow). After two weeks of HRT cessation (C), the density has regressed yielding an appearance similar to the baseline study. Reprinted with permission from Harvey JA, Pinkerton JV, Herman CR. Short Term Cessation of Hormone Replacement Therapy Decreases Recommendations for Breast Biopsy. *Journal of the National Cancer Institute*. 1997;89:1623-1625.

CONCLUSION

Hormone replacement therapy induces an increase in mammographic breast density and an increase in the incidence of benign masses, including fibroadenomas and cysts. These mammographic changes decrease specificity and sensitivity, but do not significantly increase cost. In addition, women with HRT-induced increase in breast density may be at an increased risk for developing breast cancer, and studies are underway to investigate this possibility. However, unlike most breast cancer risk factors, breast density can be influenced by such means as changing HRT type or dose, or switching to a SERM.

The author has revealed the following potential conflict of interest: PI/Consultant: Besins-ISCOVESCO, USA (produce 4-OHT gel)

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LOSS OF LIBIDO IN THE POSTMENOPAUSE

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INTRODUCTION

Loss of libido is the most frequent complaint of the Female Sexual Disorders (FSD). Population data indicate a prevalence of 33% in women between 18 and 59 years of age,[1] that reaches 76% in clinical samples, particularly after the menopause,[2] although figures vary greatly among studies due to methodological biases. Unbiased prevalence estimates from population samples have been rare, and incidence estimates have been non-existent. Until the recently convened "International Consensus Development Conference on Female Sexual Dysfunction"[3] where an interdisciplinary consensus conference panel consisting of 19 world experts in FSD expanded nosographic criteria to include both psychogenic and organic causes of desire, arousal, orgasm, and sexual pain disorders, there has been a lack of standard uniformly applied definitions of FSD. Thus there has been difficulty in measuring FSD in non-clinical samples. Concurrent with this delay and poor attention to the biological causes of FSD, diagnostic criteria have focused most on psychodynamic and psychosocial factors,[2,4] with substantial dismissal of the biological ones. The result is that whilst the uroandrologist is "the" expert of male sexual disorders, the gynecologist is virtually absent from the diagnostic scenario of FSD, that relies most on psychosexologists, with a dramatic absence of the potentially treatable medical causes of FSD. This paper is therefore devoted to suggest a more comprehensive diagnostic approach to the loss of libido, with a specific medical perspective hopefully useful to the gynecologist in his/her daily practice.

THE PHYSIOLOGIC SCENARIO

Libido, with its synonyms - sexual appetite, desire and drive, sexual impulse and interest - indicates the main sexual appetitive feeling that motivates a person to obtain sex and focuses his/her attention on that goal.[5,6] The basic drive is biologically rooted in the instinctual - rhinecephalic and limbic - brain, which is strongly hormone-dependent[5,6,8,9] and represents the core of sexual behavior. In our species the biological drive is progressively enriched by emotional and affective meanings[10-14] that seem to be particularly relevant to women. The subjective experience of being "turned on" is accompanied by and partly consists of various physiological changes, many of which are in preparation for sexual behavior .[5-7,15,16] This sexually activated mental state may be set against and influenced by the mood of the moment,[5,11,13-14] all the more in the perimenopausal transition, when mood disorders may reverberate on and cripple libido[8,13,14] in spite of the availability of a willing partner. In recent years, research on libido has grown to include a deeper understanding of its biological roots,[5-8,15-18] both endocrine and neurochemical, the motivational and relational components,[2,10-14] and its vulnerability to personal factors[19] and external agents.

Menopause may represent a critical turning point of libido as biological, motivational-affective, and cognitive factors[10] may all undergo deep changes. Motivation to engage in intercourse loses the primary biological goal, reproduction, but may well maintain the pursuit of pleasure, the "recreational sex"[8,12] as well as the "instrumental sex," when sex is performed as a means to obtain advantages and express motivations different from pleasure and/or procreation.[20]

THE DIAGNOSTIC WORK-UP

Loss of libido is multifaceted: it might be caused by biological,[5-9,16-18] motivational-affective, and cognitive factors [10,11,19,20] that may partly overlap, leading to a progressive decrease of sexual drive that parallels the process of aging.

When a woman complains of a loss of libido after the menopause, the very first step for the clinician is to define the complaint with a few appropriate questions[12,19] and exams. A useful set of questions is:[12,19] How do you feel? Do you feel comfortable with yourself, specifically with your body image? Do you feel that physical menopausal changes might have affected your sex drive or that this loss of libido might be more dependent on psychological or couple problems? These quite open questions help to address the sexual complaint in a comprehensive way, focusing on how the woman perceives the causes of her problem, secondary to the potential general impact of menopause on body shape and body image, and/or to mood disorders or frank depression, that may contribute to reduce the self-perception as an object of desire, or to frank couple problems.

It is also useful to enter the medical diagnosis of the sexual problem in a gentle and respectful way: Focusing on your libido, do you have erotic dreams, sexual day dreams, and/or voluntary sex fantasies? If yes, this indicates a usually good hormonal profile as well a substantial integrity of the mental sexual processes. Relational problems, with selective and partner-linked loss of libido, might be the real problem.[10-12] If not, this suggests that biologic as well as psychologic factors are in play. Do you suffer vaginal dryness, say difficulty in lubrication in spite of a normal foreplay? Do you feel pain during intercourse?[21,22] Do you have difficulty in reaching orgasm? If not, endocrine, vascular, and muscular problems (levator ani hypertonicity till frank vaginismus) can be reasonably excluded (although a careful physical exam is always to be recommended). If yes, a number of biologic factors should be evaluated: hormonal profile[13,14,23-26,28] and pelvic floor status,[21,22] including clitoral, vulvar and mucosal trophism.[29-31] The question "where do you feel pain?" is critical, as the site of pain during accurate pelvic exam is the strongest predictor of the organicity of pain[22] and helps to make an etiologic diagnosis. Recent data suggest that vascular risk factors (smoking, hypercholesterolemia, atherosclerosis, diabetes) might be important and usually unrecognized cofactors of arousal disorders in women, leading to secondary loss of libido.[31]

Vaginal dryness is the sexual complaint more specifically dependent on estrogen deprivation[17,14,16-18] that may concur with vascular problems[31] and/or pre-existing or actual arousal disorders[7] to the impairment of the lubrication/congestive genital response. Pelvic floor status may relate to the arousal disorder and secondary loss of libido by two main mechanisms: hypertonicity, until frank vaginismus,[8,21,22,32] when the recurrent pain becomes the strongest inhibiting factor of the wish and will to behave sexually,[21,22] mostly when tender and/or trigger points at the insertion of the levator ani on the spine worsen the physical pain during intercourse;[32] hypotonicity, more frequent in pluriparae, that is usually associated with the complaint of vaginal hypoanesthesia ("I feel nothing during intercourse"), leading to vaginal anorgasmia and sexual dissatisfaction.[8,12,16] After the menopause, the worsening effects of the loss of estrogen on the continence mechanism may concur to the arousal disorders and avoidance of intercourse for fear that loss of urine may happen during sex play.[8] Appropriate retraining of the pelvic floor disorders, either hyper or hypotonus, is mandatory to restore normal levator ani muscle tonus and correct this important and underdiagnosed physical cause of secondary loss of libido.

Is there any autoerotic activity, with orgasm? If yes, this indicates good libido, good relationship with one's body, and lack of inhibition (only when compulsive it may indicate psychosexual and/or psychiatric problems). The loss of libido might therefore be secondary to relational problems (including the real desirability of the partner), or impossibility to intercourse for partner's physical or sexual problems.[8]

Do you prefer sexual contacts to be non-coitus oriented, or only tender and loving, with physical intimacy without overt sexual meanings? This may suggest phobic aversive attitude toward intercourse, and/or sexual pain-related disorder that should be looked for (vestibulitis, vaginitis, vulvitis, vaginismus, post-coital cystitis, clitoralgia, either spontaneous or after arousal and congestion) which may cause a secondary loss of libido. Sometimes the sexual pain-related problems started years before the consultation and the patient does not recognize this etiological correlation until the accurate medical diagnosis put events in the correct etiological sequence. What is the frequency of intercourse? This rather rough indicator should be better analyzed, evaluating motivation to intercourse (i.e., on acceptance of partner's initiative and pressure, instead of for personal drive), quality of arousal, presence or not of orgasm, and quality of satisfaction or dissatisfaction after it.

The clinician should be comfortable with these quite intimate questions, choosing the ones that he/she feels more at ease with. With time, proper training, and familiarity with this issue, this clinical history will be rewarding in terms of diagnostic accuracy, patient satisfaction (for the quality and pertinence of the assessment), and improvement of doctor-patient relationship.

If the clinical history suggests a possible biological etiology, the gynecologist should: A) assess the patient's hormonal equilibrium; B) assess the trophism of the pelvic floor structures; and C) assess psychobiologic factors.

A) ASSESSMENT OF PATIENT'S HORMONAL EQUILIBRIUM

There are three common situations: the woman is naturally menopausal and is not taking hormone replacement therapy (HRT). The loss of libido is usually gradual over time, is accompanied by the complaint of vaginal dryness, for the reduced action of the Vasointestinal Peptide (VIP) secondary to the loss of estrogen[16] until frank dyspareunia[8,12,17,21,22] and of an increased difficulty to achieve coital orgasm. "I do not recognize myself anymore" is a frequent report, in spite of a stable and satisfying relational life. Central (depression and insomnia, that may be worsened by the loss of sexual hormones)[11-14] and peripheral etiologic factors (pelvic floor involution secondary to menopause)[21,29] may overlap and contribute to a complex impairment of the sexual response, of which the loss of libido is just the tip of the iceberg and the symptom more easily reported in consultation. Well tailored HRT usually restores premenopausal sexuality, if other negative biological, personal, or relational factors are not in play. For the woman who has

undergone surgical menopause, her loss of libido typically has a sudden onset, within the first months after bilateral oophorectomy which on average deprives the woman of 50% of her androgen production.[23-26] Androgens are credited to be the strongest biologic supporters of libido, although human sexuality remains strongly "context-dependent."[27] After ovariectomy, a cohort of accompanying symptoms is usually reported: loss of libido, reduced vital energy, reduced assertiveness (that may mimic but are not depressive symptoms), loss of pubic hair, and diminished muscle mass, leading to a specific "Female Androgen Deficiency Syndrome" (FADS),[28] that well indicates how the androgen loss might have central[5,9,15,26,28,33] as well as peripheral effect.[29-31] Androgen replacement therapy increases libido in women who are androgen-deficient (e.g. after surgical menopause)[23,24,26,28] but it does not seem to affect sexual arousal and behavior in naturally menopausal women:[25] i.e., physiological replacement of deficient plasma levels may restore libido, whilst supplementation to supra-physiologic levels does not (but it may increase side-effects, which are likely to be dose-dependent).

Androgens could have a threefold action: increase susceptibility to psychosexual stimulation, contributing to the "sexually activated mental state" typical of a good libido;[5-7,15,23-28] increase sensitivity of the external genitalia, facilitating the nitric oxide pathways that leads to clitoral congestion;[29,31] and increase the intensity of sexual gratification.[26,28] Unfortunately, optimal HRT guidelines for systemic or topical treatment have not been produced in controlled studies thus far. Topical testosterone cream is an approved treatment of vulvar lichen planus.[29] It has been claimed to improve clitoral sensitivity, heighten arousal, and ease clitoral orgasm, thus leading to a higher sexual satisfaction that might enhance libido, but controlled studies are still lacking.

Sometimes a woman complains of low libido, in spite of a good marital relationship, good health, and a well tailored HRT. She might be suffering from a mild FADS, as oral estrogens may increase Sex Hormone Binding Globulin (SHBG),[30] thus reducing the free testosterone available for biological activity. In these cases, the clinician should prescribe a dosage of free testosterone: if low, a well tailored androgenic replacement might prove helpful. Prolactin assessment is also correct, as a persistent prolactin increase has an inhibiting effect on libido and on the sexual cascade of neurovegetative and vascular responses, via the dopaminergic system.[9,15]

In summary, consolidated evidence suggests that hormones, in their complex interplay, seem to control the intensity of libido and sexual behavior, rather than its direction,[10] which is more dependent on motivational-affective and cognitive factors. Estrogens contribute to the maintenance of secondary sex characters, to the central and peripheral scenario of femininity, that can be thrilled and lit up by appropriate levels of androgens, whilst prolactin may inhibit the physiologic cascade of events involved in the sexual response.

Among new perspectives of research, two deserve to be mentioned. First, oxytocin is considered the most important neurochemical factor that links the affective and the erotic quality of bonding[15] involved in libido itself, but its clinical usefulness in FSD diagnosis and treatment has not been assessed.

Second, the post-menopausal sex-hormones-dependent involution of sensory organs, that are sexual targets and sexual determinants of libido,[6,8] might be an important and thus far dismissed biological contributor of loss of libido in the aging woman.[8,18] A pleasant oral intimacy dramatically increases libido and arousal in women. Vice-versa, hormone dependent mouth dryness[34,36] may impair the physiologic increase of salivary secretion during foreplay. Mouth dryness has been reported in 45% of healthy post-menopausal women, up to 60% of those taking modifications other than HRT,[36] but its impact on oral intimacy impairment has curiously not been investigated. The same involution interests the olfactory epithelium[37-38] that might concur to loss of libido for the reduced sensitivity to pheromones and the skin.[39,40] Symptoms suggestive of this involution – reduced olfactory sensitivity,[37,38] mouth drynes,[34-36] and skin altered sensitivity ("touch impaired disorders" according to Sarrel and Whitehead[41]) – might stress the role of the physical factors in loss of libido and encourage a more assertive HRT to restore a better responsive body.

B) ASSESSMENT OF TROPHISM OF THE PELVIC FLOOR STRUCTURES

Accurate evaluation of the external genitalia may reveal involutional changes of the clitoris that may relate to the loss of genital sensations after the menopause.[29] Twenty percent of postmenopausal women express it with the shocking expression "My clitoris is dead" in the Sarrel and Whitehead series.[41] A biological correlate has recently been suggested. The clitoral cavernosal erectile tissue consists of smooth muscle and connective tissue. Tarcan et al[42] utilized computer assisted histomorphometric image analysis to determine the age-associated changes in clitoral cavernosal content of smooth muscle and connective tissue in clitorises obtained from fresh cadavers (age 11 to 90 years) and from patients undergoing clitoral surgery (age 6 months to 15 years). The percentage of clitoral cavernosal smooth muscle in the age group of 6 months to 15 years was 65+/-1.5; in 44 to 54 years it was 50+/-1.2; and in 55 to 90 years was 37+/-1.3 (ANOVA p=0.0001). This study revealed a strong link between increase in age and decreased clitoral cavernosal smooth muscle fibers, which may play an as yet undetermined pathophysiology in age-associated clitoral sexual dysfunction.

Vaginal trophism[7,14,21] as well as the tonus of the perivaginal muscle[32] should routinely be assessed, more so if a sexual complaint is reported in consultation. Accurate differential diagnosis of etiological factors leading to sexual pain-related disorders is mandatory, as genital pain is one of the strongest inhibitors of sexual drive in women.[21,22]

C) ASSESSMENT OF PSYCHO-BIOLOGIC FACTORS

The gynecologist should briefly investigate psychobiologic factors for a comprehensive diagnosis and a pertinent referral to a psychosexologist, if indicated. The erotic sense of femininity may suffer a major insult from the menopause, particularly in women who are used to relying on their beauty and self-image to nourish their self-esteem and the self-confidence in the courting play; this is why at least a few questions of the clinical history should focus on potential changes in self-perception. Mood disorders,[5,10,13,14] depression and anxiety,[5,13,14] chronic stress and insomnia[8] typical of a symptomatic menopause can further contribute to the loss of libido, impairing both its biological and motivational dimensions. Addiction (alcohol and tobacco first) may

contribute to FSD, and their potential role should be investigated.[9]

Finally, motivational-affective and cognitive factors should be briefly investigated. Relational factors, implications and quality of couple relationship,[10,12,19] partner's attitude and problems, erectile deficit first, and his real desirability,[8] may further modulate the intensity and direction of libido and contribute to the contradictory findings in the variability of libido in perimenopausal years.[43] Male sexual disorders, which increase dramatically with age, might cause dysfunctional FSD in up to 62% of partners according to Renshaw.[44] This long-lasting dissatisfaction may further contribute to female loss of desire[45] until complete sexual inactivity is reached and partly explain why 70% of women over 60 are sexually inactive.[1]

CONCLUSION

Loss of libido is a multifaceted disorder increasingly reported during the gynecological consultation, particularly during and after the menopause.[8,11,13,14,23-26,30,31,44,46] The physician should first assess the potential role of hormonal factors, loss of estrogens and, specifically, of androgens, that trigger both libido and arousal, central and peripheral, and/or potential increase of prolactin that may further inhibit libido. Second, he/she should focus on quality of sexual response, as arousal disorders, dyspareunia, orgasmic difficulties, dissatisfaction, both physical and emotional, may contribute to a secondary loss of libido, where biological and motivational factors overlap. The gynecologist should specifically diagnose pelvic floor dysfunctions and genital anatomic factors that may lead to a disappointing physical response.[21,22,29-32] The diagnostic work-up should also recognize psychobiologic factors that may interfere with the motivational-affective bases of sexual response, namely depression, anxiety, chronic stress, and insomnia, all of which may be worsened after the menopause. The potential role of relational conflicts and/or marital delusions and partner-specific problems, erectile deficit first, should be finally assessed, to effectively address treatment of the libido disorder.

The gynecologist may greatly contribute to reduction of the biological causes of loss of libido, through a well-tailored HRT, including androgens in selected cases; improvement of genital physical dysfunctions and associated FSD; adequate treatment of depression, anxiety, and insomnia that may all concur to reduce the sex drive; and encouragement of healthier lifestyle (reducing cholesterol and smoking, with their damaging vascular effect, and alcohol for its negative effect on mood and libido). The psychosexologist will better address motivational and relational factors, if present, once the physical equilibrium has been restored.

REFERENCES

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