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Mammographic Breast Density and Hormone Replacement Therapy

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INTRODUCTION

Mammographic or parenchymal breast density refers to the radiologic appearance of the breast, which varies considerably among women due to differences in the proportion of fat, connective, and epithelial tissue.[1] Fat is radiologically lucent and appears dark in mammograms. Connective and epithelial tissues are radiologically dense and appear light, an appearance that is referred to as mammographic densities. Mammograms with significant parenchymal density are generally more difficult to read than those with little density. On average, premenopausal women generally have denser breasts than postmenopausal women, which contributes to decreased sensitivity screening mammographies in women under the age of 50 years.[2]

Use of hormone replacement therapy (HRT), including therapy with either unopposed estrogen or estrogen plus progestin, increases breast density in some postmenopausal women shortly after the initiation of treatment.[3–5] This change in breast density has led to some speculation that mammographic detection of cancer may be compromised in HRT users.[3,6,7] However, researchers have shown that detection of breast cancer is not impaired by HRT use.[8] Moreover, advances in mammographic technology are improving the sensitivity and specificity of even the most difficult-to-read mammograms.[9,10]

Reports of a relationship between higher levels of mammographic density and greater risk of breast cancer[1,10,11] have stimulated further interest in understanding any connection between breast density and HRT. While the reasons for the association between breast density and breast cancer risk remain unclear, some investigators have suggested that increases in breast density induced by HRT might increase a woman's risk for breast cancer.[4,12] However, to date no studies have addressed whether HRT-induced increases in breast density are associated with an increased risk of breast cancer. Further, there is a marked inconsistency of results from close to 60 epidemiologic studies that have examined HRT and breast cancer risk.[13] This inconsistency suggests either no effect or, at best, a weak effect of HRT on the risk for breast cancer.[13] Nonetheless, awareness of HRT-induced changes in breast density is growing among clinicians as well as patients, while the clinical significance of these changes remains unclear. This paper will review research on breast density and postmenopausal hormone therapy and any known association with breast cancer risk.

FROM THE EDITOR

David F. Archer, M.D.

James V. Fiorica, M.D., presents the current status of hormone therapy and mammography density. He concludes that although hormones increase mammographic breast density, there is no evidence for a decreased or impaired detection of breast lesions.

Anne H. Calhoun, M.D., identifies the problems associated with hormone therapy and migraine headaches. The association with estrogen, or as presented the changes in estrogen serum levels, often leaves the physician prescribing hormone therapy with the need for a therapeutic trial. Modification of hormone therapy is based on the outcome of the migraine headaches' frequency and intensity. This article presents a means of circumventing the need for modification by picking a constant regimen of estrogen in advance.

Benjamin C. Wong, M.D., describes the vulvovaginal symptoms related to estrogen withdrawal, in postmenopausal women which consist of itching, burning, and dryness. Despite being on oral hormone therapy, approximately that 30% to 40% of women require local estrogen for relief of symptoms.

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FACTORS THAT INFLUENCE BREAST DENSITY

Multiple factors influence breast density including age, weight, height, parity, menopausal status, age at first birth, and age at menarche.[14,15] Breast density is also affected by the luteal phase of the menstrual cycle in premenopausal women[16] and HRT use in postmenopausal women.[17] Of these factors, the effect of age on breast density is probably the most widely recognized. Numerous studies show that as women age, mammographic density decreases due to losses of glandular, ductal, and fibrous connective tissue accompanied by relative increases in fatty tissue.[15,18–20] Table 1 highlights age-related changes in breast density, with significant reductions in the proportion of lean tissue evident around the time of the menopause.

Age and parity only partially explain the wide variability in breast parenchymal patterns among women.[17] Research is needed to identify additional factors that determine the degree of breast density. For example, the influence of genetic factors and gene-environment interactions on breast density is a potentially important area of study that has received little attention.[21] Investigation of genetic determinants of breast density may provide further insight on the nature of any association between breast density and breast cancer risk.

BREAST DENSITYAND BREAST CANCER RISK

A number of investigators have reported that women with the highest levels of breast density have greater risk for breast cancer, compared with women with very little breast density,[10,11,22,23] although the nature of the relationship between the two variables is unclear. In a study that included both pre- and postmenopausal women, Byrne and colleagues[11] found that those with a breast percent density (the ratio of the area of breast density to the total breast area) of 75% or greater had an almost five-fold increased risk of breast cancer compared with women with no visible breast density. The explanation for this association has been elusive, with no evidence to date for either a direct causal pathway or the existence of factors that independently affect both breast density and breast cancer risk (i.e., the increased cancer risk may be due to one or more factors which also influence breast density). In addition, it is clear that breast cancer develops in a large number of women who do not have mammographic parenchymal patterns associated with increased risk.[10]

The results from a recent study of breast density by race and age further demonstrate how little is known about the relationship between breast cancer risk and mammographic density. In their examination of screening mammograms from more than 28,000 women aged 20 to 79 years, El-Bastawissi *et al*[24] found that variations in breast density by race and age did not conform to variations in breast cancer risk by race and age. Asian and African American women in this study had greater breast density than Caucasian women, while breast density among Native American and Hispanic women was similar to that of Caucasian women. However, compared with non-Hispanic Caucasian women, the age-adjusted incidence rate of breast cancer was 15% lower for African American women, 38% lower for Asian and Hispanic women, and 71% lower for Native American women.

Table 1. Distribution of Mammographic Breast Density by Age (N = 28,984)

	Breast Density*			
Age	**Almost Entirely Fat (n = 2,524)**	**Scattered Fibro-glandularTissue (n = 12,028)**	**Heterogeneously Dense (n = 10,935)**	**Extremely Dense (n = 3,497)**
≤45 years	4.2%	28.9%	43.0%	24.0%
46–55 years	6.3%	37.5%	41.8%	14.1%
56–65 years	10.6%	48.7%	34.5%	6.2%
≤66 years	14.2%	51.1%	30.5%	4.3%

*BI-RADS™ classification. The Breast Imaging Reporting and Data System from the American College of Radiology. Values are percent of total women in each age group.
Adapted from El-Bastawissi *et al*.[24]

HRT AND BREAST DENSITY

Observational studies that compared mammograms before and after starting HRT have shown that use of HRT increases mammographic density in some women. Most studies that have quantitated HRT-induced changes show that fewer than one-third of women experience an increase in breast density on postmenopausal HRT (Table 2),[4,25–31] although some studies reported higher figures.[32–35] The reason for these varied results is likely multifactorial, involving patient demographics, regimen type, and often subjective monitoring procedures.

Table 2. Summary of Studies of HRT and Mammographic Densities

Study	Design	Assessment	Hormone Use	n	Pertinent Results
Lundström *et al*, 2001[35]	Observational	Wolfe patterns	Continous HRT	52	33% increased density at first visit according to Wolfe classification
			Oral estrogen	51	
			Transdermal estrogen	55	2% increased density at first visit according to Wolfe classification
					2% increased density at first visit according to Wolfe classification
Rutter *et al*, 2001[3]	Observational	BI-RADS	HRT users	335	Increase in density with initiation or continued use; decrease in density upon cessation
			HRT past-users	111	
			Nonusers	2,942	
Freedman *et al*, 2001[25]	RCT	Computer assisted	Estrogen only	36	1.2% mean increase in density over baseline values
Sterns and Zee, 2000[26]	Observational	Visual interpretation	HRT	443	8% of HRT users increased density. HRT typically maintained density present at the time of initiation, density decreased with age in nonusers.
			Nonusers	789	
Greendale *et al*, 1999[4]	Observational	BI-RADS	Continuous HRT	67	19.4% of subjects increased density within 1 year
			Cyclic HRT-MP	55	16.4% of subjects increased density within 1 year
			Cyclic HRT-MPA	51	23.5% of subjects increased density within 1 year
			Estrogen only	58	3.5% of subjects increased density within 1 year
			Placebo	64	0% of subjects increased density within 1 year
Lunström *et al*, 1999[34]	Observational	Wolfe patterns	Continuous HRT	50	52% of subjects increased density
			Cyclic HRT	75	13% of subjects increased density
			Estrogen only	50	18% of subjects increased density
Ozdemir *et al*, 1999[32]	Observational	Visual interpretation	HRT (four regimens)	88	34% of subjects demonstrated increased density
			Control	30	0% of control group demonstrated increased density
Marugg *et al*, 1997[31]	Retrospective	Wolfe classification	HRT	58	31% increased breast density
			Estrogen only	23	9% increased breast density
Persson *et al*, 1997[5]	Observational	Visual interpretation	Cyclic HRT	136	10% increased density
			Continuous HRT	103	28% increased density
			Estrogen only	314	5% increased density
			Nonusers	554	3% increased density
Erel *et al*, 1996[27]	Retrospective	Visual interpretation	HRT	73	11% of all subjects demonstrated increased density, regardless of type or duration of hormone treatment
			Estrogen only	35	
Laya *et al*, 1995[33]	Observational	Wolfe patterns	HRT	41	24% increased density after 1 year according to Wolfe classification
McNicholas *et al*, 1994[30]	Observational	Visual interpretation	HRT	33	27% of subjects demonstrated increased density
			Control	31	0% of subjects demonstrated increased density
Stomper *et al*, 1990[29]	Retrospective	Visual interpretation	HRT	38	26% of subjects demonstrated mammographic changes
			Estrogen only	12	17% of subjects demonstrated mammographic changes
Berkowitz *et al*, 1990[28]	Retrospective	Visual interpretation	HRT	16	12% of subjects demonstrated moderate increase in density
			Estrogen only	14	0% of subjects changed mammographic densities

One of the factors that may explain the variability in results depicted in Table 2 is patient age at the time of initiation of HRT. For example, Sterns and Zee[26] found an increase in breast density in only 8% of women who had initiated postmenopausal hormone therapy. Breast density remained at pretreatment levels for the majority of HRT users in this study, and this effect was particularly evident among women who had begun hormone therapy prior to age 55. For most women in the study, HRT preserved existing fibroglandular tissue in the breast when therapy was initiated close to the time of the menopause. The overall effect of HRT in these women is to prevent the loss of breast parenchyma that typically occurs after cessation of menses[26] (shown in Table 1), rather than to increase actual density proportions. The premise that HRT can delay involution of the breast when it is initiated around the menopause has also been suggested by others.[25,36]

Variability in estimates of the proportion of women with HRT-induced increases in breast density may also be attributed to differences in hormone regimens. For example, Sendag *et al*[37] reported an increase in density in women receiving continuous-combined estrogen plus progestin (31.1%) over women receiving estrogen alone (3.9%), based on the mammographies of 216 women. There were no significant density changes among women receiving cyclic estrogen-progestin or tibolone-only treatment. Among participants in the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial, increases in radiographic density occurred in 3.5% of women taking unopposed conjugated equine estrogens (CEE) and 16.4% to 23.5% of women taking CEE with a progesterone (cyclic medroxyprogesterone acetate [MPA], continuous MPA, or cyclic micronized progesterone).[4] Lundström and colleagues[35] reported similar findings in a small, unblinded study that included 158 women. When classified according to the Wolfe criteria,[38] 33% of women taking oral continuous-combined HRT experienced an increase in breast density, while only 2% of women using unopposed oral estriol or transdermal estradiol experienced an increase in density. In a randomized controlled trial, Freedman and colleagues[25] found that, after two years of unopposed estrogen therapy, one-third of women experienced an increase in breast density, but the mean change in breast density for these women was only 1.2% greater than baseline levels and was not statistically significant. Ozdemir *et al*[32] reported that 28% of women on tibolone experienced an increase in breast density after an average of 16 months of therapy. These findings show that breast density changes may be related to the individual HRT regimen.[37]

Finally, a third factor that may account for variability in mammographic screening studies is differences in methodology employed by researchers. The majority of older studies utilized subjective visual interpretation of mammograms to quantitate changes in density patterns. Recent advances both in mammographic reporting systems and in breast imaging technology have resulted in improved consistency in the interpretation of mammographic images and in discrimination among different tissue types in all women, including those with higher breast density. Future studies employing such advanced techniques should be useful in clarifying the extent to which HRT influences breast density patterns.

While the percentage of women who experience an increase in breast density with HRT use varies from study to study, the time frame for HRT-induced changes is consistent. Numerous studies have shown that, among those women who experience an increase in breast density, the increase occurs within one year after initiation of HRT.[4,26,32,34]

Using an observational cohort of naturally postmenopausal

Table 4. Detection Methods in HRT users and nonusers

Cancer Detection Method	HRT Users (n = 58)	HRT Nonusers (n = 57)
Mammography alone	66%	67%
Palpation alone	7%	9%
Mammography and palpation	28%	25%

Values are percent of total women in each group.
No statistical significance was indicated between groups in either measurement.
Adapted from Roubidoux *et al*.[8]

Table 3. Breast Cancer Stages in HRT Users and Nonusers

Cancer Stage	HRT Users (n = 58)	HRT Nonusers (n = 57)
0	26%	33%
I		
T1a	7%	42%
T1b	12%	4%
T1c	29%	14%
II	22%	25%
III	3%	19%
IV	0%	4%
Nodal metastases	19%	2%

Values are percent of total women in each group.
No statistical significance was indicated between groups in either measurement.
Adapted from Roubidoux *et al*.[8]

women, Rutter *et al*[3] showed that, compared to nonusers, women who initiated HRT were more likely to show increases in breast density (relative risk [RR], 2.57; 95% confidence interval [CI], 2.12-3.08), while women who discontinued HRT use were more likely to show decreases in density (RR, 1.81; 95% CI, 1.06-2.98). These changes in breast density are sustained as long as therapy continues.[3,26] This indicates that breast density changes associated with HRT increase with initiation and decrease with discontinuation. The effect on breast density reverses quickly after cessation of therapy, typically within two weeks.[39] This rapid reversal may allow a clinician to repeat the mammogram to evaluate mammographic concerns after a brief washout period, if desired.

BREAST CANCER DETECTION

Although some have reported reductions in mammographic sensitivity with HRT use,[7,40] others[41] have observed no significant differences in the sensitivity of screening mammography among HRT users and never-users (96% and 91%, respectively). Importantly, a potential for slight reductions in mammographic sensitivity with HRT does not necessarily translate into a difference in cancer detection between HRT users and nonusers. For example, if HRT use indeed lowers the sensitivity of mammographic screens, it would be expected that higher-stage tumors or more palpable cancers would be found in HRT users. However, when Roubidoux and colleagues[8] compared the breast cancer stages and detection methods in users and nonusers with breast cancer (Tables 3 and 4), they found no significant differences in cancer stages or in the number of mammographically detected cancers with HRT use, in agreement with others.[42]

The most compelling evidence for the absence of a deleterious effect of HRT on breast cancer detection comes from studies that compare tumor biology among HRT users and nonusers who develop breast cancer. The results from these studies consistently show that breast cancers among HRT users are detected at earlier stages than breast cancers among nonusers,[43,44] a finding that is incompatible with the suggestion that HRT impairs breast cancer detection. A greater frequency of lower-grade tumors has been documented even in studies with no differences in mammography rates among hormone users and nonusers or when the data are adjusted for the method of detection.[45–53] These results may explain, in part, findings from observational studies which suggest a reduction in breast cancer mortality rates among HRT users.[45,46,54–62] All-cause mortality rates are also consistently lower among postmenopausal hormone users compared with nonusers.[55,56,60,61,63,64] While an association between breast density and breast cancer risk has been observed in some studies that have included both pre- and postmenopausal women,[10,11,22] there have been no reports that address the effect of HRT-induced rapidly reversible changes in breast density and breast cancer risk. In addition, the findings from close to 60 observational studies of HRT and breast cancer risk are inconclusive.[13]

SUMMARY

Although postmenopausal hormone therapy increases breast density in some women, if administered early in menopause, HRT maintains premenopausal breast density and prevents age-associated losses in fibroglandular tissue. Research has shown that breast cancer detection is not impaired by HRT use, and in fact, breast cancer in women using HRT is often detected earlier than in women not using HRT. Although definitive answers about breast cancer risk and hormone use remain elusive, the lack of conclusive findings of increased breast cancer risk and the consistently lower mortality rates among HRT users suggest that if there is an effect of HRT on breast cancer, it is small. The influence of HRT on mammography should play a minor role in the decision to take HRT.

The author has revealed the following potential conflict of interest:
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REFERENCES

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Understanding and Managing the Hormonal Migraine

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INTRODUCTION

Migraine is a far more common condition in women than many physicians appreciate. The accepted and frequently quoted statistic that migraine affects 18% of women (vs. 6% of men) does not take into account its prominent peak at midlife, when it impacts roughly 30% of reproductive-aged women. It is much less common before puberty and typically improves after menopause.[1] If we examine lifetime prevalence by age 50, however, migraine has affected up to 40.9% of women.[2] During the reproductive years, the gender ratio exceeds 3:1 female to male. In fact, this predominance of headache in women and its associated clinical, social, and economic burden makes it one of the most important medical issues in women's health.

Migraines are episodic disabling headaches that may last four to 72 hours and are accompanied either by nausea or by photophobia and phonophobia. Migraine without aura occurs more frequently (85%) than migraine with aura (15%). Sufferers experience a spectrum of headache types in addition to migraine, including episodic tension-type headache and migrainous headache. The majority of migraineurs are undiagnosed, commonly mislabeling their headaches "sick" headaches, "menstrual" headaches, or "sinus" headaches (due to migraine's frequent predilection for the ophthalmic or maxillary divisions of the trigeminal nerve — where it may present as either unilateral or bilateral pain).

The relationship of migraine to hormonal events in women has long been clinically appreciated. Its emergence often coincides with the onset of cyclic hormonal events at puberty and its easing with the hormonal stability of menopause. Commonly, migraines will abate during

the last two trimesters of pregnancy.[3] Premenopausally, the headaches occur more commonly with the onset of menses or in the two days preceding the onset of menses than at other times in the menstrual cycle.[4] However it is migraine's seemingly unpredictable, but often robust, response to starting, stopping, or changing oral contraceptives or hormone replacement therapy (HRT) that has engendered a host of anecdotal empiric strategies. Unfortunately, in the face of worsening migraines, a frequent strategy is simply to stop all exogenous hormone therapy and forego its benefits or indications.

GENERAL TREATMENT CONSIDERATIONS

Treatment of the hormonal migraine, in concept, is identical to treatment of any migraine:

(1) Improve the "background."

This involves avoidance of known triggers; stopping over-usage of analgesics, decongestants, or caffeine; and improving sleep habits.

A not uncommon complication of migraine is to undergo a transformation into chronic headaches. These headaches, often with tension-type characteristics, are present 15 or more days a month. This transformation can occur as a result of analgesic or decongestant overuse — the so-called "rebound headaches." Practical advice would be to limit use of these products to two days a week or less.

(2) Treat the acute migraine effectively.

Ten years ago, the abortive treatment of migraine was revolutionized by development of the serotonin receptor 1B/1D agonists. The therapeutic activity of these agents, known as triptans, can be attributed to their selective activity on serotonin receptors on intracranial blood vessels and the trigeminal nerve. Activation of these receptors causes vasoconstriction of abnormally dilated intracranial vessels and inhibition of neurogenic inflammation. The majority of patients treated early with these agents are able to resume normal activities within two hours.

Prior to the development of these agents, the acute treatment of migraine relied largely on potent analgesics, ergots, and bedrest.

Currently available triptans in the United States include sumatriptan, zolmitriptan, rizatriptan, naratriptan, and almotriptan, with eletriptan and frovatriptan soon to be released. The triptans carry Category C labeling for use in pregnancy.

(3) Consider prophylaxis when headaches are still frequent and/or severe.

Only here, the therapy of the hormonal migraine may diverge from treatment of other migraines. The concept is still the same — to offer preventive therapy for headaches that are still troublesome after the first two steps have been addressed. The difference is that in menstrual or other hormonal migraines, there is a specific trigger — falls in estradiol — that can be targeted with hormonal manipulation.

Beyond hormonal manipulation is the usual armamentarium for migraine prophylaxis, including beta blockers and anticonvulsants. The choice of preventative therapy should be individualized to the patient and her symptoms or comorbidities (e.g., hypertension, depression, asthma, seizure disorder).

THE ESTROGEN CONNECTION

To understand the menstrual or hormonal migraine, one must first examine the relationship of migraine to female sex hormones. From studies in the literature, five unifying hypotheses can be proposed which will predict a migraine's response to hormonal changes and serve as a template for designing a variety of successful strategies. The hypotheses are:

(1) Falls in circulating estradiol concentrations are causally associated with the menstrual migraine.

In the mid-1970s, Somerville demonstrated experimentally that migraines occurred with falls in estrogen.[5] He measured perimenstrual estradiol levels in subjects with a history of menstrual migraine, and then injected estradiol valerate six days before the anticipated menses. Estradiol levels rose and were sustained for about a week and a half. The injections postponed the usual "menstrual" migraine until the estradiol valerate levels dropped several days after the onset of menses.

This relationship, migraine coinciding with falls in estradiol, fits with clinical observation. Women tend to experience migraines at times when estrogen falls, such as with the menses, immediately after ovulation, after delivery, early in the placebo week of an oral contraceptive, and during falls in estradiol levels with HRT.

(2) Progesterone's role in migraine is negligible.

Somerville also experimented with progesterone supplementation. The extension of luteal phase progesterone levels was followed by menstrual bleeding when progesterone fell; but this bore no apparent temporal relationship to migraine.[6] The subjects still had their migraines when estradiol levels fell.

(3) Eliminating the premenstrual fall in estrogen will prevent the menstrual migraine.

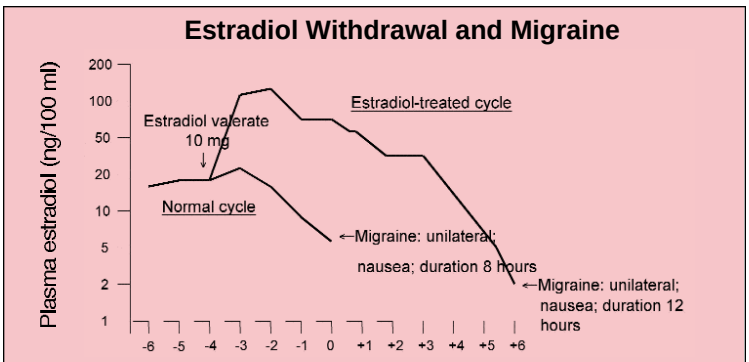
Sustained *high* levels of estrogen are beneficial: 24 menstrual migraine patients were treated for up to five years with subcutaneous estradiol implants. Norethisterone was given for seven days each month to induce withdrawal bleeding. Twenty-three of the 24 patients improved with the treatment, 20 becoming completely or almost-completely headache-free. Implants provided sustained elevation of estradiol at a mean concentration of 600 pmol/L, levels that inhibited ovulation.[7]

Sustained *low* levels of estradiol are equally beneficial: gonadotropin-releasing hormone agonists (GnRH-a) have been used to suppress ovarian steroid production in women with menstrual migraine. Leuprolide acetate was given IM for 10 months, achieving a hypogonadal state in all the subjects (estradiol averaged 15.5 pg/mL). Migraines were markedly diminished in the subjects for the duration of the treatment.[8]

Sustained *physiologic* levels of estradiol are beneficial: during the last six months of the leuprolide trial, continuous estrogen-progestin was "added-back." Estradiol levels averaged 64.0 pg/mL, levels typically seen with postmenopausal HRT. It was equally successful in significantly and markedly diminishing their migraines.[8]

The key is that in all of these situations, the fluctuations in estradiol levels were eliminated. The tendency for migraines to be better before puberty and after menopause is also in accord with this hypothesis. The absence of ovulatory and menstrual declines in estradiol predicts the observed decrease in migraine frequency.

Similar to childhood and menopause, pregnancy is a time marked both by lack of estrogen decreases and improvement in migraine. Migraines may briefly worsen at the end of the first trimester, possibly



Adapted from Somerville BW. *Neurology*. 1972;22:355-365.[5]

corresponding with the decline in HCG. However, with the sustained building of estrogen throughout the second and third trimesters, migraines may remit completely until after delivery.

(4) Reducing the endogenous or exogenous falls in estrogen can lessen or prevent migraine.

Estradiol gel has been studied for menstrual migraine prophylaxis. Applied percutaneously for several days to supplement late luteal phase estradiol levels, a 1.5 mg estradiol gel was moderately successful in reducing menstrual migraine.[9]

With similar trials utilizing transdermal patch therapy, the 0.025 mg and the 0.05 mg estradiol patch applied perimenstrually were ineffective for migraine prophylaxis. However, a 0.1 mg patch was comparable in efficacy to the gel studies.[10] The higher dose patch increases estradiol levels to about 75 pg/mL, similar to the successful gel therapy studies. The low dose patch gives only a 20-pg/mL increment. There was no significant benefit from a 0.05 mg patch in a double blind, placebo-controlled trial. All of these studies likewise fit the fourth strategic hypothesis: reduction in the decline in estradiol lessens or prevents the headache.

Although it has been suggested that a serum estradiol level of 60-80 pg/mL is required perimenstrually to prevent menstrual migraine, it is unlikely that any absolute estradiol level is "protective." Rather, there may be a threshold for the magnitude of the fall in estrogen that can be experienced by an individual migraineur without provoking an attack.

(5) Increasing the magnitude of the falls will make migraine worse.

Controversy exists over the use of "low dose" contraceptives with migraine. A frequently-quoted study concluded that these pills made migraine worse.[11] The pill used in that study was Ovral®, a norgestrel pill containing 50 µg of ethinyl estradiol (EE). Although in 1977 this was considered "low dose," 50 µg pills are now the highest dose available in the United States and account for only 4% of today's domestic oral contraceptive market.

In a blinded crossover study, the 50-microgram pill was associated with an increased frequency of moderate and severe headaches.[11] These results are in keeping with the fifth hypothesis, that increasing the magnitude of the fall in estrogen intensifies the migraine. Fifty micrograms of ethinyl estradiol is a supraphysiologic dose of estrogen. (The late luteal phase decline in estradiol that is associated with menstrual migraine is arguably equivalent to 25 µg of ethinyl estradiol.) The placebo week of Ovral®, therefore, allows for a precipitous, and *twice* physiologic, fall in estradiol. The fifth hypothesis would, therefore, have predicted a worse-than-usual menstrual migraine.

Estradiol has several important effects in the central nervous system, which may underlie and help explain its relationship to migraine. When estrogen falls, the production of serotonin also declines, and its rate of elimination increases (through increases in monoamine oxidase). The sensitivity of 5HT1 receptors, which is important to the triptan agents' function, decreases. Endogenous opioid activity declines with a decrease in the concentration of pain-relieving ß-endorphins.[12]

Often the hormonal storm of the perimenopause exacerbates migraine. Falls in estradiol before the menses can be so low as to produce not only cyclic hot flashes but cyclic sleep disruptions as well, further aggravating migraine. Low estradiol is associated with significant decreases in deep (slow-wave) sleep and REM sleep. Migraine has a close connectedness to sleep centers, with the dorsal raphe (the serotonergic slow-wave sleep center) and the locus ceruleus (the noradrenergic REM sleep center) often referred to as the "migraine generator," the focus of initial activity during a migraine.

SPECIFIC HORMONAL STRATEGIES

With the hypotheses in mind, therapeutic approaches would aim to reduce falls in endogenous or exogenous estradiol.

In the perimenopausal migraineur, one strategy is to utilize a 20 µg oral contraceptive (OC) administered at bedtime with a lower dose of estrogen added back on days 22-28, in place of the placebo pills.[13] Sample regimens include any of the following in place of the placebo pills (or in the case of Mircette®, in place of the placebo/active pills of the fourth week):

- Conjugated equine estrogens 0.9-1.25 mg at bedtime days 22-28
- Esterified estrogens 1.25 mg at bedtime days 22-28.
- 17 ß-estradiol 1-2 mg at bedtime days 22-28.
- transdermal 17 ß-estradiol 0.075-0.1, applied days 22 (a.m.) and 25 (p.m.).

Alternatively, long-cycle (active-pill only) therapy could be initiated with uniphasic OCs for nine to12 weeks. The patient could then be withdrawn to a 0.1 µg estradiol patch for five to seven days before resuming long-cycle therapy. This would be a particularly attractive strategy for the woman with co-morbid dysmenorrhea.

For smokers over age 35, or in other women in whom OCs might have relative contraindications, perimenstrually applied estradiol patches could be considered: a 0.1 mg 17 ß-estradiol patch could be applied two days before the expected date of menses or one day before the expected date of menstrual migraine.

For severe and refractory cases, consideration could be given to administration of gonadotropin releasing hormone agonists (GNRH-a).

Although migraineurs typically improve at menopause, certain hormone therapy regimens may negate this improvement. Interrupted estrogen therapy, with days off at the end of the month, is classically associated with migraines on the "off days." Patients on ERT or HRT patch therapy should be questioned about headache symptoms on the day preceding patch changes. Patients experiencing migraines before a seven-day patch change could be switched to twice-weekly patches, changed Sunday morning and Wednesday evening to better divide the week. Monthly injections of estradiol and/or testosterone typically give supraphysiologic rises in estradiol in the first week after injection with significant falls before

the next dose. Migraineurs on these regimens often report significant worsening of their headache pattern with "explosive" migraines before injections.

Fine-tuning of strategies to reduce falls in estradiol require consideration of the metabolism of the active hormone, primarily through cytochrome P450 3A4. Medications that increase the enzyme's activity could create daily falls during oral therapy. Cigarette smoking increases all hepatic oxidative enzymes and could consequently lead to similar falls.

Examining the intrinsic pharmacokinetics of the different ERT/HRT preparations reveals differences in T_{max} and half-life. Consideration could be given to dividing the dose of the more rapidly metabolized oral estrogens for the migraineur. There is certainly rationale for avoiding morning dosing of oral estrogens. If a major trigger of migraine is a dropping estradiol level, and the lowest threshold for migraine is in the morning, it is reasonable not to want the two to coincide. Bedtime administration is preferred for HRT or OCs.

RISKS AND BENEFITS OF HORMONAL THERAPY IN MIGRAINEURS

The use of oral contraceptives has been controversial in women with migraine, as the stated risk of stroke in migraineurs is approximately twice that of nonmigraineurs, though the absolute risk remains quite small. An increased risk of stroke with OCs was first reported in the high-dose (50-150 µg) pills of four decades ago, but a correlation of estrogen doses to stroke could not be made in that study since 23 of the 25 women with thrombotic stroke on mestranol-formulation OCs took pills containing the 100 µg dose.[14]

More recent reviews and studies of nonsmoking normotensive women on OCs (30-35 µg EE) do not show these risks. Petitti *et al*[15] conducted a population-based case-control study of stroke in today's low-dose OC users. A total of 408 confirmed strokes occurred in 1.1 million women during 3.6 million woman-years of observation (reaffirming that stroke is rare in women of childbearing age.) Although stroke risk was increased with the independent variables of smoking, hypertension, or diabetes, there was no increased risk associated with use of low-dose OCs. A study investigating coagulation parameters in 20 µg pills, compared with 30 µg and 35 µg pills, showed a dose-response effect. Importantly, no changes in hemostasis parameters were seen in nonsmokers using the 20 µg pill.[16]

Even accepting a possibly increased relative risk of stroke (but small absolute risk), benefits to the migraineur would in most instances outweigh any risk. These benefits notably include a reduced risk of epithelial ovarian cancer and endometrial cancer, as well as the symptomatic improvement of menometrorrhagia, dysmenorrhea, and ovarian cysts.

It could be argued that the menstrual fall in estradiol itself is not beneficial for a segment of the population at risk for vascular ischemia. Whereas physiologic levels of estradiol appear to be vasodilatory (with purported mechanisms including improved endothelial function mediated by nitric oxide[17], calcium channel blockade[18], angiotensin converting enzyme inhibition[19], and alterations in sympathetic tone[20]), acute depletion of estradiol is associated with vasomotor instability. Premenopausal women with coronary disease appear to be at highest risk for coronary ischemia with the menstrual fall in estradiol,[21] a time when migraineurs would be most likely to be treated with triptans or ergotamines.

IHS Criteria for Migraine

Headache with any two of the following:

- Moderate-to-severe intensity
- Pulsatile (however, 50% are steady)
- Unilateral (41% are bilateral)
- Exacerbated by activity

Accompanied by either:

- Nausea (±vomiting) (fewer than 30% vomit)
- Photophobia & phonophobia

Adapted from International Headache Society Guidelines.

CONCLUSION

In conclusion, migraine is a common and largely undiagnosed problem in reproductive-aged women. Its responses to both endogenous and exogenous changes in estrogen, however, are predictable. With understanding of the fundamental relationships, a variety of successful strategies can be drafted to eliminate or reduce hormonal triggers of the menstrual migraine or the migraine associated with therapeutic hormonal regimens.

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Atrophic Vaginitis

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INTRODUCTION

Atrophic vaginitis, also referred to as urogenital atrophy or senile vaginitis in the literature, refers to inflammation or irritation of the vagina due to estrogen deprivation in postmenopausal women. Although it is mainly a clinical entity in the postmenopausal age group, it can also occur in other conditions associated with relative estrogen deficiency including, but not limited to, premenarche, postpartum, lactation, and use of medications such as GnRH agonists that suppress endogenous estrogen production. The prevalence of atrophic vaginitis has been reported to be as high as 40% to 50% by Greendale *et al*[1] and Notelovitz in postmenopausal women.[2] Hence, atrophic vaginitis can contribute to significant morbidity in this age group.

In premenopausal women, estrogens maintain vaginal colonization with lactobacilli, which produce lactic acid from vaginal glycogen, thus maintaining a low vaginal pH. Decreased estrogen production leads to atrophy of the vagina, loss of glycogen, and increased pH when lactobacilli are lacking. The inhibition of other potential vaginal pathogens is therefore reduced, leading to an increase in pathogenic bacteria. The vagina is predisposed to infection by streptococci, staphylococci, coliforms, and diptheroids. Inflammation or irritation caused by an inflammatory response to erosions in friable tissues or secondary bacterial infection can in turn lead to symptoms of burning and pruritus. The mucosa of the distal urethra is also rich in estrogen receptors, which is consistent with its common embryologic origin with the vagina. Withdrawal of estrogen can cause irritative urinary symptoms, such as frequency and urgency due to changes in the urethral epithelium.

There are significant changes based on histology in the vagina of the postmenopausal woman. The superficial and intermediate cell layers of the vaginal epithelium are reduced in thickness and associated with proliferation of connective tissue, fragmentation of elastin, and hyalinization of collagen. Small ulcers with acute inflammation and granulation tissue may be interspersed among regions of intact epithelium. Leukocyte and plasma cell infiltration is evident in the submucosa. This histologic pattern can occasionally be confused with high-grade squamous intraepithelial lesions.[3]

The pathogenesis of the symptoms of burning and itching in atrophic vaginitis has not been fully elucidated. Discrepancy occurs between patients' symptoms and physical findings on examination.[4] The timing of onset of vaginal atrophy symptoms with respect to time since menopause also varies from one woman to another.[5] It may occur as late as 10 years after menopause in some women. It appears that factors such as cigarette smoking promote the findings of vaginal atrophy,[6] while greater endogenous levels of androgens reduce the severity of symptoms.[7] Further research is needed to identify other modulators, both endogenous and exogenous, that could contribute to the pathogenesis of atrophic vaginitis.

Common complaints of atrophic vaginitis include pruritus, burning, local discomfort, dyspareunia, discharge, and bleeding. As mentioned, urinary symptoms such as dysuria, urgency, and frequency can also occur. Jalbuena reported the prevalence of symptoms and signs of pruritus to be 61%, dryness 58%, dyspareunia 56%, vaginal discharge 56%, dysuria 22%, burning or soreness 22%, and urinary tract infection 35%.[8] Physical examination of the vagina shows a loss of vaginal rugae, pink pale epithelium with a dry, glazed appearance, and a variable degree of erythema. Petechiae and ecchymoses may also be visible and present. The vaginal epithelium is thin and relatively avascular and inelastic. The pH of vaginal secretions is typically > 5.0 (normal < 4.5 in premenopausal women). Wet mount microscopy of vaginal secretions can show white blood cells and immature vaginal epithelial cells with relatively large nuclei.

One of the goals of the history and physical is to rule out other causes of the symptoms. Diseases such as vulvar intraepithelial neoplasia, lichen sclerosus, and local chemical irritation from perfumes, soaps, etc., can cause similar irritative symptoms but will require different management. If bleeding is the main complaint, other sources of bleeding such as uterine, cervical, or rectal causes need to be ruled out. Endometrial biopsy is indicated if there is a concern that the uterus is the source of the bleeding. Trichomonas vaginitis, bacterial vaginosis, and less often vulvovaginal candidiasis may be superimposed upon atrophic vaginitis and require specific treatment if present. A vaginal culture should be performed for those patients with a purulent discharge and cervical cultures or DNA probes obtained for Neisseria gonorrheae and Chlamydia trachomatis when indicated based on the history and physical findings. Any secondary vaginal infection should be treated in the usual fashion.

THERAPY OF ATROPHIC VAGINITIS

There are several approaches to management of atrophic vaginitis. All patients should be given instructions for vulvovaginal hygiene (Table 1). Sexual activity has been shown to be beneficial in maintaining vulvovaginal health in postmenopausal women and therefore should not be discouraged. Leiblum *et al* has demonstrated the negative association between coital activity and symptoms of vaginal atrophy.[7] In a prospective study of 23 postmenopausal women receiving oral or vaginal conjugated equine estrogens, women who were sexually active showed a greater decline in pH levels.[9] The presumed mechanism is that sexual activity improves and maintains vaginal blood flow. Vaginal lubricants such as Replens®, Astroglide®, or K-Y® are useful in those women with a complaint of vaginal dryness. Since the etiology of the vaginal atrophy is the hypoestrogenic

Table 1. Vulvovaginal Hygiene Measures

- No douches, perfumes, bubble baths, feminine deodorant products, or soap in the vulvovaginal area.
- Rinse all undergarments thoroughly after laundry.
- Wear loose-fitting cotton underwear.
- Use only cotton pads; avoid synthetic materials.

state, hormone replacement therapy (HRT) is a logical approach. The two main routes of administration are systemic (oral and transdermal) and vaginal. Systemic HRT may not be required for treatment of vulvovaginal symptoms alone. However, due to the reduced amount of estrogen absorbed from the vagina into the systemic circulation compared to oral or transdermal administration, patients may not get full systemic benefit of HRT. On the other hand, there is evidence that patients on systemic estrogen replacement therapy (ERT) can benefit from the addition of vaginal therapy if their vulvovaginal symptoms do not completely subside on systemic treatment.

Systemic ERT has proven beneficial in alleviating symptoms of atrophic vaginitis. The data are mainly based on studies done using oral preparations. A literature review failed to identify any studies of the efficacy of transdermal ERT for the treatment of atrophic vaginitis. Oral ERT has been shown to reverse the physical findings of atrophic vaginitis including the presence of a caruncle, areas of redness of the vaginal epithelium, the background color of the epithelium (pink versus pale), and the visibility of blood vessels on the epithelium surface,[10] vaginal pH, and vaginal cytology.[9] Vaginal blood flow also increased significantly over the first year of use, and the improvement continued even beyond that point.[9] There was significant increase in the recovery of lactobacilli in vaginal cultures following treatment.[11] Systemic ERT can have limitations in treating vaginal symptoms. Standard systemic ERT may not eliminate the symptoms of atrophic vaginitis in up to 25% of women.[12] Even after 24 months of therapy, some patients do not fully respond to systemic therapy alone for vaginal atrophic symptoms.[13] In these patients, addition of vaginal ERT can be beneficial, as discussed below.

Benefits of local ERT in treatment of atrophic vaginitis and related urogenital symptoms have been documented. Vaginal ERT is especially useful among patients who have contraindication for systemic therapy or experience side effects from systemic therapy. In addition, there is a role for the addition of vaginal ERT in women already on oral or transdermal ERT. In a double-blind randomized placebo-controlled trial, the benefits of a three-month course of 1 gm of conjugated equine estrogen vaginal cream on alternate days in treating 67 patients with urinary urgency and evidence of trigonitis on cystourethroscopy were noted.[14] Among these women, 37 were already on some form of systemic ERT and their baseline vaginal pH was significantly lower than those not using estrogens. Further lowering of vaginal pH and decrease in mean parabasal cell count of the lateral vaginal wall occurred with the addition of the vaginal estrogen. Vaginal administration of estrogen resulted in a more favorable clinical response, even in women already on oral ERT.

"Even after 24 months of therapy, some patients do not fully respond to systemic therapy alone for vaginal atrophic symptoms. In these patients, addition of vaginal ERT can be beneficial, as discussed below."

In another study, 43% of postmenopausal women with vulvovaginal symptoms had persistent complaints while receiving systemic therapy and benefited from additional local vaginal estrogen.[8] A greater subjective response of urogenital symptoms was noted when estrogen was given vaginally compared to orally.[15] Vaginal estrogen therapy appears to provide relief much faster by producing better local effects. Patients with symptoms of atrophic vaginitis may be started on both oral and vaginal estrogen to achieve faster relief in symptoms until systemic effects of the oral preparation take effect.

Several different preparations are available for vaginal use, including creams (Premarin Vaginal Cream®, Estrace Cream®, and estriol cream), tablets (Vagifem®), and estrogen-releasing vaginal ring (Estring®). The recommended dosages are outlined in Table 2. Estriol cream is not commercially available in the United States but is available in Europe. The dose that has been used in a European study was 0.5 mg daily for the first two weeks followed by a maintenance dose of 0.5 mg three times weekly.[16] There are no data to suggest that any one vaginal estrogen preparation is significantly more efficacious than others based on clinical end points. Patients who do not tolerate one vaginal estrogen preparation can be placed on a trial of another. Once symptoms of vaginal atrophy are controlled, therapy may then be further tapered to the most infrequent dosing that maintains healthy vaginal epithelium or relieves the symptoms.

Conjugated estrogen vaginal cream (Premarin®) at the concentration of 0.625 mg/g can be applied intravaginally daily at bedtime at a dose of one-eighth of an applicator (0.5 g) for four weeks and then twice a week. Patients who experience irritation with vaginal cream may tolerate 0.1% estradiol vaginal tablets (Vagifem®) at a dose of 25 µg per day. Based on the data in a multicenter, open-label, randomized, parallel group study by Rioux *et al*, 25 µg 17ß-estradiol vaginal tablets are equivalent to 1.25 mg of Premarin Vaginal Cream® in relieving symptoms of vaginitis.[17] There were no appreciable systemic estradiol increases or estrogenic side effects with the use of Vagifem® and it appears to have greater patient acceptance and lower withdrawal rates compared with Premarin Vaginal Cream®.

Daily intravaginal administration of 25 µg and 50 µg estradiol provided similar changes in vaginal cytology and clinical efficacy.[18] A dose as low as 10 µg of vaginal estradiol is effective in controlling symptoms of urogenital atrophy, including urinary frequency, urgency, urge incontinence, dyspareunia, vaginal dryness, and vulvovaginal pruritus and burning without causing endometrial hyperplasia or increased systemic estradiol levels.[19]

Comparison between estradiol vaginal tablets and estriol vaginal suppositories has shown similar effectiveness in treating vaginal pruritus, irritation, dryness, and dyspareunia in a European study.[20] A pronounced improvement in vaginal and urethral karyopyknotic index was noted following daily treatment with estriol 0.5 mg.[21]

Effectiveness of estrogen deficiency symptom relief and the reduction of urogenital atrophy in postmenopausal women with administration of Estring® has been documented by a multicenter randomized

trial.[22] This low dose 17ß-estradiol delivery system consists of a core containing 2 mg of 17ß-estradiol within a silicone polymer in a ring shape designed to fit in the vagina. The estradiol release rate is determined by the rate of diffusion through the silicone membrane and remains constant at 7.5 µg/24 hour for a period of 90 days. Estring® offers the convenience of not needing to take daily medication either orally or vaginally. It is therefore especially beneficial to patients who have difficulty in remembering to take their medication on a regular basis. The vaginal ring does not interfere with coitus. One of the drawbacks of the Estring® is that it may not stay in the vagina for patients with significant prolapse.

POTENTIAL ENDOMETRIAL EFFECTS OF VAGINAL ESTROGEN

Endometrial proliferation and hyperplasia have been reported after vaginal administration of conjugated estrogen[17] as well as estriol and dienoestrol.[23] Depending on the preparation, a significant amount of the medication may be absorbed into the systemic circulation. Vaginal estrogen cream results in similar plasma estrogen levels compared to oral administration.[24] A pharmacokinetic study of Vagifem® showed significant estradiol absorption after administration of 10 µg and 25 µg of 17ß-estradiol, followed by a decline of absorption with both doses after 14 days.[25] The initial high rate of absorption is presumed to be due to the ready absorption through a thin atrophic vaginal epithelium. The proliferative effect of estrogen on the endometrium is both a result of its level in the systemic circulation and its direct local effect when it is administered in proximity to the uterus. A more recent study showed that the systemic absorption of estradiol from low doses (10 µg and 25 µg) of vaginal estradiol tablets was low in the majority of women but not all.[26] Fewer patients on unopposed vaginal estradiol tablets 25 µg per day experienced endometrial proliferation or hyperplasia compared with patients who were using unopposed conjugated equine estrogen vaginal cream 1.25 mg per day.[17] In this study, one of the 80 women on vaginal estradiol had proliferative endometrium, and two of the 79 women on conjugated equine estrogen vaginal cream had endometrial hyperplasia along with seven others with proliferative endometrium. Although several studies have included the assessment of endometrial development as one of the secondary outcomes in women on vaginal estradiol, or on a lower dose of vaginal conjugated equine estrogen therapy, and found no endometrial proliferation with unopposed vaginal estrogen replacement, these reports should be discounted as valid safety studies. The follow-up periods were not long enough and the numbers of patients in the study were small with reference to the expected time of development for and incidence of endometrial hyperplasia or malignancy.[19, 20, 27, 28] In his review, Archer concluded that chronic administration of any dose of vaginal estrogen could lead to an increased risk of endometrial cancer.[29] A case-control study investigating the risk of endometrial cancer in users of low-potency estrogen noted a weak association (OR = 1.4; 95% CI = 1.0-2.0) between vaginal application of low-potency estrogen and risk of endometrial cancer.[30] The small number of cases limited the power of the study, and the association may have been significant if a large sample size had been used. Until further safety data is available for the use of unopposed vaginal estrogen therapy, clinicians should consider the use of progesterone or progestin therapy in women with an intact uterus and receiving vaginal ERT.

SUMMARY

In conclusion, estrogen deprivation in postmenopausal women leads to several physiologic changes in the vagina and renders them susceptible to urogenital irritation and secondary bacterial infection. ERT improves both the symptoms and signs of atrophic vaginitis. Vaginal administration of ERT appears to be superior to systemic administration in the postmenopausal population. Women on vaginal ERT who have a uterus should be considered for concomitant progesterone or progestin therapy to avoid the potential effect of unopposed estrogen in the endometrium.

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Table 2. Recommended Dosages for Vaginal Estrogen Preparations as Described in the *Physicians Desk Reference® 2002*

Estrogen Preparation	Starting Dose	Maintenance Dose
Premarin Vaginal Cream® 0.625 mg/g	1-2 g daily for 1-2 weeks	0.5-1 g 1-3 times a week
Estrace Vaginal Cream® 0.01% (0.1 mg/g)	2-4 g daily for 1-2 weeks	1 g 1-3 times a week
Vagifem® 25 µg vaginal tablet	1 tablet daily for 2 weeks	1 tablet twice weekly
Estring® 2 mg ring	Replace every 90 days	

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