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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Sexuality in Post-Menopausal Women



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INTRODUCTION

There is some concern among the lay public that the medical profession has attempted to medicalize menopause. To some degree this may be true, but it is for good reason; health care providers are generally interested in promoting health in the mature (postmenopausal) woman. Sexuality is a unique area in this regard because there is a vast under utilization of hormone replacement therapy (HRT) in most instances, and there is still considerable inappropriate use in others. There is over reliance on androgen therapy (AT) to increase libido for hypoactive female desire-phase dysfunction. There is also tremendous under utilization of estrogen replacement therapy (ERT) to prevent genital atrophy: preserving the epithelial integrity of urogenital tissues is a prerequisite for adequate arousal in females. This article attempts to simplify the informational morass of hormone therapy and sexual function in the mature female.

Masters and Johnson¹ described the classic representation of the human sexual response cycle in 1966 as an orderly progression from excitement-plateau-orgasm-resolution. Kaplan² later appropriately modified this progression by dividing the excitement phase into a desire phase and an arousal phase, and by eliminating the plateau phase as a specific entity. This lin-

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ear progression of the sexual response cycle remains the template for the "Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition" (DSM-IV) classification of sexual dysfunction currently in use (Figure 1).³ This nosology has a major flaw in that it implies an orderly, linear progression of phases whereas there is now well-recognized evidence of an interdependence between phases in females, just as there is in males.

Physiologically, the sexual response cycle is quite similar in males and females. For instance, arousal (erection in males and lubrication in females) normally occurs as a consequence of vasocongestion in the pelvis within 15 to 25 seconds after appropriate erotic stimulation. The orgasmic response is also biologically identical in males and females. Typically, both groups experience eight to 12 contractions of the levator muscle, occurring at precisely 0.8-second intervals. Because the biology of the cycle is so similar in men and women, the "slower" response rate seen in females in western culture represents more of a learned behavioral response than a biologic difference. To illustrate, in cultures where the majority of young females masturbate, there is no difference in cycle length between men and women.

The division of the excitation phase of the sexual response cycle into a desire and an arousal phase is important both

FROM THE EDITOR

David F. Archer, M.D.

Dr. Ronald Ross presents the data on HRT and breast cancer risk in a meticulous fashion. His presentation identifies and excludes confounding factors that could introduce bias into his study. There is limited information on the role of progesterone and progestogen in the induction or growth of breast cancer. There are strong advocates on both sides of the discussion of HRT and breast cancer (see Speroff L, *Menopausal Medicine*, Spring 2000). Clinicians must take all of the data into account when counseling their patients.

Dr. Murray Freedman clearly identifies that the interpersonal relationship rather than hormones is responsible for hypoactive desire phase dysfunction in female sexuality. A major goal for hormone replacement therapy is to prevent or restore atrophic changes in the genital tract because of the significant contribution of vaginal atrophy to avoidance of sexual activity.

Dr. Janice Rymer brings to our attention a new pro drug known as Tibolone (Livial), which has been used outside the United States for HRT over the past 5+ years. There is clinical evidence of the efficacy in reducing menopausal symptoms and maintenance of bone mineral density. Associated with its use is a significant decrease in the occurrence of uterine bleeding and endometrial stimulation. This article serves as a preview for our readers of this product's anticipated introduction into the U.S. marketplace.

Menopausal Medicine

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biologically and therapeutically. The desire phase is primarily a cognitive (central) function, while arousal is more of a physical (peripheral) event. There is clearly a higher amplitude of libido in men because of high levels of circulating testosterone, and a hypoactive desire phase in most reproductive age men is extremely unusual. Conversely, as men age, they experience considerable arousal phase dysfunction, largely on a physical basis. There is, however, tremendous interdependence between the phases. This becomes especially obvious in mature men who develop an organic arousal phase dysfunction, or “erectile dysfunction,” when performance anxiety (i.e., “spectatoring”) compounds the original peripheral organic defect by superimposing a deleterious central effect. Conversely, there is a peripheral “reflex arc” effect wherein tactile stimulation peripherally augments arousal in the absence of significant central stimulation. This has been demonstrated in paraplegics, in whom direct penile stimulation greatly facilitates orgasm. There is usually an interdependence between central and peripheral effects, but in females, it is widely recognized that cognitive function dominates responsiveness. This central dominance in women probably represents a combination of proscriptive sociocultural training and biology (i.e., lower testosterone levels).

In females, structures derived from the urogenital sinus – the urethra, trigone, and vagina – have the highest concentration of

Figure 1
Female Sexual Dysfunction

Sexual Desire Disorders
Hypoactive sexual desire disorders
Sexual aversion disorder

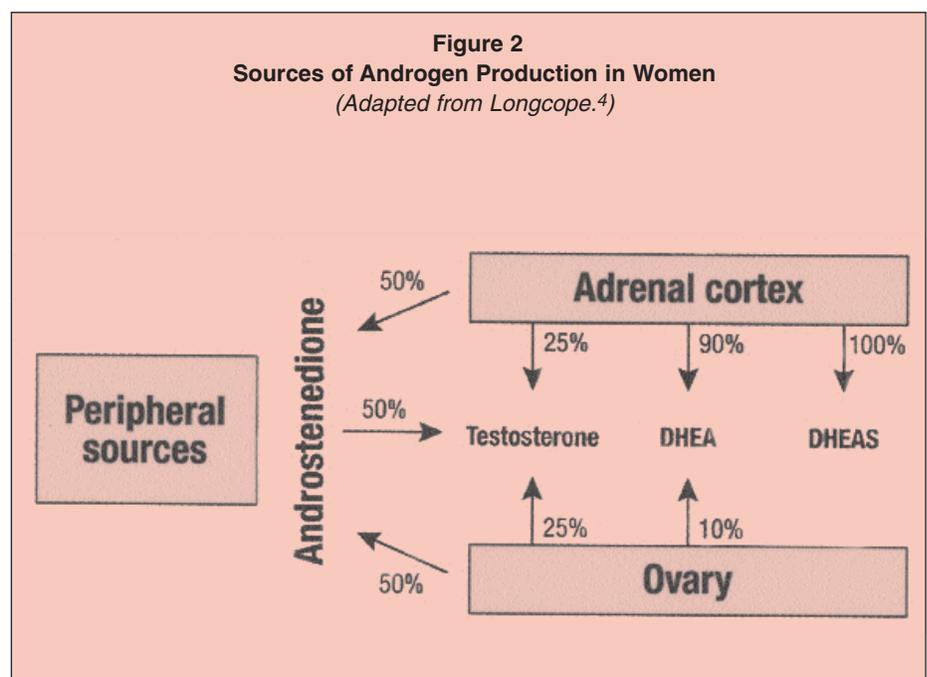
Sexual Arousal Disorders
Partial or total lack of physical response

Orgasmic Disorder
Persistent delay or absence of orgasm

Sexual Pain Disorders
Dyspareunia
Vaginismus

Sexual Dysfunction Not Otherwise Specified
Modified DSM-IV classification.³

estrogen receptors in the human body. Estrogen deficiency leads to marked genital atrophy over time, but lubrication becomes compromised rather rapidly because the healthy epithelium and vaginal ecosystem are so dependent on estrogen. It is particularly important to treat vaginal atrophy early on and thereby prevent dyspareunia. Otherwise, disuse atrophy can compound the problem of genital atrophy associated with estrogen deficiency. Just as rapid atrophic changes in the vaginal epithelium occur as a result of



estrogen deficiency, local therapy can reestablish a beautifully estrogenized epithelium within as little time as six to eight weeks. It is unfortunate indeed that arousal phase dysfunction in older men is not so amenable to therapy.

The maintenance of a healthy, functional urogenital tract and the prevention of sexual and urinary dysfunction represent major areas in which HRT is underutilized. The deeper, atrophic interstitial changes in the genital tract associated with estrogen deficiency after menopause (vascular, neural, and connective tissue alterations) are more insidious in onset and require years to manifest. Consequently, they require longer-term HRT to reverse than do the superficial epithelial changes, and like osteoporosis, the changes become irreversible over time.

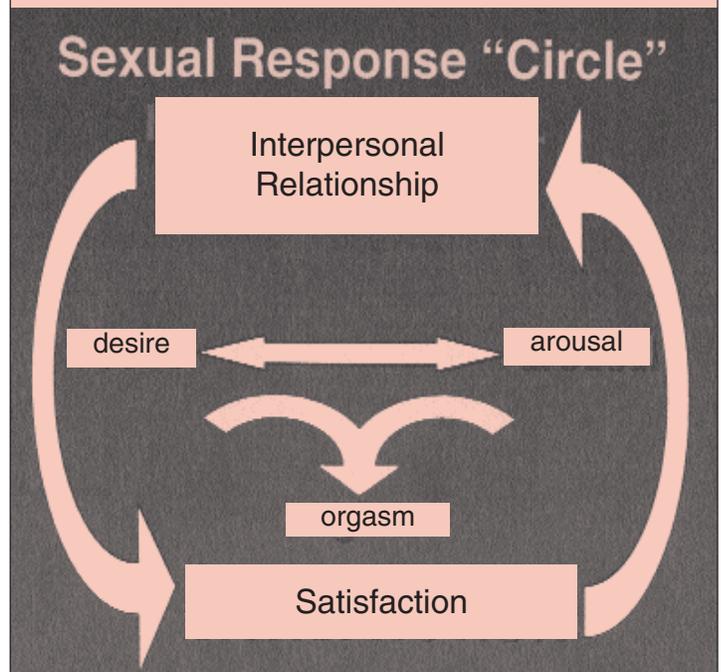
The over-reliance upon androgen therapy (AT) for most hypoactive desire-phase dysfunction in women is as striking as the specific under-utilization of ERT for the prevention of genital atrophy. It is the interpersonal relationship rather than hormonal imbalance that is responsible for most hypoactive desire phase dysfunction in women, both pre- and postmenopausally. Nevertheless, there are instances of hypoactive desire in females as a direct result of a relative androgen insufficiency.

Although it is an egregious oversimplification, a relative deficiency of “free” testosterone in the female can contribute to decreased libido. This is especially true

in the ovariectomized woman, in whom significant androgen production from the postmenopausal ovarian stroma has been acutely eliminated. Figure 2 illustrates the production of androgens in the reproductive-age female.⁴ Figure 3 depicts that while the normal postmenopausal production of testosterone only declines from 250 mg to 180 mg, the ovarian stroma is the predominant source of circulating testosterone in the postmenopausal woman.^{4,5}

Oftentimes, the continued, albeit diminished, adrenal androgen production (and its metabolites) maintains sufficient circulating testosterone to perpetuate normal libido.⁶ It is noteworthy that oral ERT induces an increase in serum levels of sex hormone binding globulin (SHBG) which may create an iatrogenically induced dysfunction by reducing “free” testosterone below the woman’s therapeutic threshold.

Figure 4
Sexual Response “Circle”
(MA Freedman 2000)



In such women, androgen supplementation to ERT is extremely efficacious in restoring diminished libido.⁷ A similar phenomenon is seen occasionally in women taking oral contraceptives as a result of the increase in SHBG. The unanswered question in such patients is which form of AT is the best form of replacement. This is a complex question because augmenting libido directly probably requires the aromatization of testosterone to estrogen in the brain. Because oral alkylated androgens, such as methyltestosterone, are not aromatizable to testosterone, their effect is indirect by lowering SHBG and increasing the available circulating “free” testosterone.

There is good evidence in the literature that the administration of parenteral testosterone has a direct, central effect on libido, but serum testosterone levels have been supraphysiologic in many of these patients. Shifrin et al⁸ reported recently that use of transdermal testosterone improved sexual function while increasing androgens only slightly. In another recent study, patients who reported sexual dysfunction and demonstrated laboratory evidence of androgen deficiency responded well to AT while maintaining physiologic levels of hormones.⁹

There is also growing evidence that androgens act peripherally in arousal and

Figure 3
Decline in Androgen Production After Menopause
(Adapted from Loncope⁴ and Adashi.⁵)

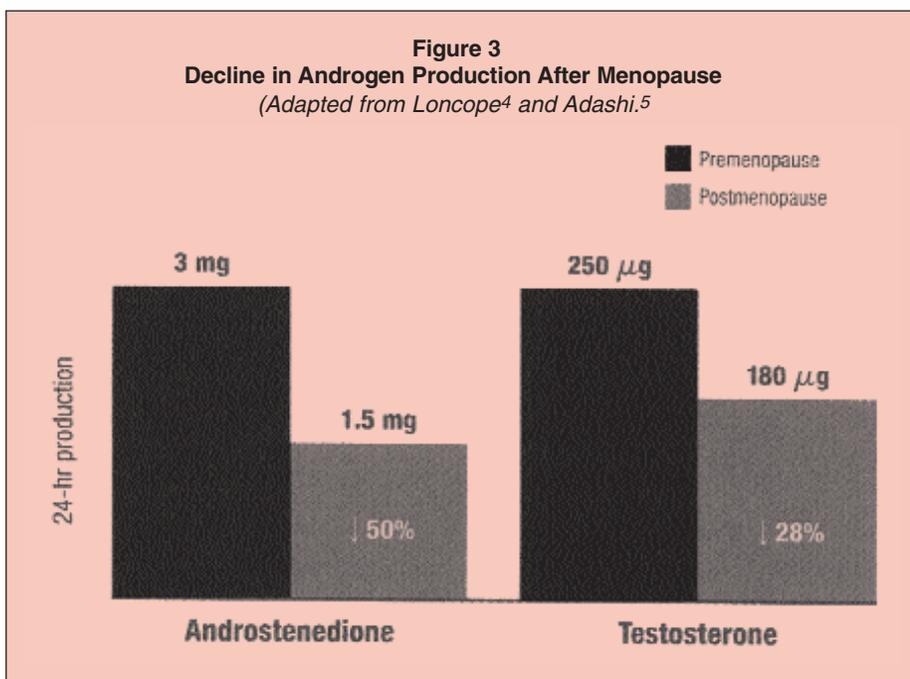


Figure 5
Reported Satisfaction Levels of
Couples Having Sex at Least
Once/Week (%)

Extremely happy	78
Very happy	58
Generally satisfied	48
Sometimes fairly happy	35
Unhappy most of the time	27

(Adapted from Michael RT 1994.¹²)

not just centrally for desire. In addition to vasoactive peptides, androgens also appear to be responsible for relaxation of genital smooth muscle involved in the arousal response in both sexes.¹⁰ This finding represents yet another example of the physiologic synergy between the desire and arousal phases of the female sexual response cycle.

The role of HRT in relation to genitourinary atrophy should not be restricted solely to the prevention and treatment of urinary and sexual dysfunctions; it should be directed toward preserving genital integrity and enhancing normal function.

This quality-of-life issue for women deserves far more attention than it currently receives. Few males would electively pass up the opportunity to delay involutinal changes in their genitalia. All women would glean considerable benefit from ERT in regard to genital atrophy, and a growing body of evidence suggests that a subset may benefit from AT as well. Sildenafil (Viagra) is but the first of many vasoactive agents to be introduced that enhance nitric oxide activity and complement a declining arousal phase in men...and being estrogen replete should be a prerequisite for the sexually active female partner.

Freedman,⁶ Basson,¹¹ and Leiblum¹² all have recently emphasized the importance of including satisfaction as an essential component of the sexual response cycle. Instead of a linear relationship with orgasm as the endpoint, a cyclic concept with satisfaction as the focus is more appropriate for females (Figure 4). Women, whether by nature, nurture, or both, are giving and accommodating. Because of this orientation, satis-

faction might even be supplanted by gratification, which implies partnered sex and mutual pleasure. Humans are distinctly sentient beings, and for women, the interpersonal relationship is the quintessential factor in sexuality.

Happiness is an attitude, not an event. While an orgasm can be an intense, pleasurable event, it adds little to one's overall happiness. Unhappy people, especially those who become depressed, are much more likely to experience a sexual dysfunction, and there are good data substantiating that happy people have sex more often (Figure 5).¹³ Psychologists agree that a rewarding, active sex life contributes to happiness, compared with the absence of an active sex life. Sexuality obviously encompasses much more than orgasm per se, and for females, the interpersonal relationship is the key to motivation.

In males, the dominant factor determining sexuality is biologic; a twenty-fold increase in testosterone level occurs at puberty.¹⁴ The classic paradigm of human sexuality as the combination of one's biology, psychology, and sociology needs to be revised to include the interpersonal relationship and satisfaction. In Dennerstein's longitudinal study of Australian women during the 10-year menopausal transition (45 to 55 years old), 61% noticed no overall change in their sexuality, 32% noticed a decline, and 7% noticed an increase.¹⁵ The most common finding in the group noting an

increase in activity? A new partner! The influence of the interpersonal relationship is not solely a female phenomenon; males with erectile dysfunction also experience this cognitive influence.

Another aspect of sexuality that is frequently overlooked is the augmentation of the "normal" response . . . not just the treatment of dysfunction. Happiness involves much more than simply the absence of displeasure or discomfort. In a recent report of self-assessed sexual well-being among 1,030 females (Figure 6), Bancroft at the Kinsey Institute found that "general well-being" was the most important variable determining satisfaction among females, ranking ahead of "subjective sexual experience, attractiveness of partner, and sexual response" for example.¹⁶

CONCLUSION

There is growing support for the concept that female sexual desire is predominantly an emotional-/intimacy-based phenomenon. While the spinal cord has a "reflex arc" and all the elements necessary for the complete sexual response cycle, the female genital response is still largely controlled by supraspinal centers in the brain. The modern concept of the female sexual response cycle, thus, should be circular, with the emphasis on interpersonal relationships and satisfaction (gratification), rather than orgasm. Furthermore, what mature adult, male and female alike, wouldn't warmly embrace a complementary medication that arrests genital atrophy while impacting so many other outcomes favorably? The prevention of genital atrophy deserves far more attention than it currently receives.

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Figure 6
Variables: Order of Importance

1. General well-being
2. Subjective sexual experience
3. Attractiveness of partner
4. Sexual response
5. Frequency of sexual activity
6. Partner's sensitivity
7. Subject's health
8. Partner's health

(Bancroft J. *FSDF*, Boston, MA, October 2000.¹⁵)

Ltd.; 1994.

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The Progestin Dilemma



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INTRODUCTION

Hormone replacement therapy (HRT), in the form of unopposed estrogen replacement therapy (ERT), became very popular in the United States in the late 1960s and early 1970s. The reason for this popularity is not entirely clear as little was known at that time about the short- and long-term health effects of ERT use.

Nonetheless, by 1974 there were more than 30 million prescriptions of non-contraceptive estrogens being filled annually in the U.S. The most popular brand of ERT, the conjugated equine estrogen (CEE) Premarin®, was among the three most frequently prescribed drugs in the country. In that year, however, the first reports were published demonstrating the strong association between ERT use and endometrial cancer risk, an association that was strongly predicated on duration of use and daily pill dosage. Although there was much bickering in the scientific

community regarding methodologic issues in these early studies, it soon became clear that this was, in fact, a causal association. This realization led to profound changes in HRT prescribing strategies. Overall use of ERT dropped dramatically so that within five years, use was less than half that of the peak year of 1974. For those continuing to use HRT, there was a strong tendency to reduce the daily pill dose, from a typical dose of 1.25 mg or more of CEE to 0.625 mg daily or less.

But the other major change was to rethink strategies for administering HRT so that any health benefits from HRT use could continue to be derived, but in a way that the excess endometrial cancer risk would be greatly reduced or even eliminated. In particular, clinicians began to prescribe a progestin sequentially with estrogen in monthly cycles (typically estrogen every day for 28 days with the progestin, usually medroxyprogesterone acetate in a dosage of 10 mg, added during the final 10 days, but individual physicians often designed their own variations of this schedule). Although this strategy was designed primarily to protect the endometrium from the carcinogenic effects of the estrogen, it was assumed by many physicians to be “physiologic” (i.e., mimicking the monthly cycle of hormone changes in naturally menstruating premenopausal women) and, therefore, such combination hormone replacement therapy (CHRT) was prescribed to many women who had undergone a hysterecto-

Table 1
Health Effects of Adding Progestin to ERT

- Can Eliminate Excess Endometrial Cancer
- May Enhance Slightly Beneficial Effects on Bone
- Effect on Heart Disease Risk Not Known
 - No Reason to Suspect Benefit to Heart
 - Likely to Reduce Any Beneficial Estrogen Effect
 - Lipoproteins
 - Prostaglandins
 - Vasospasm
 - Progesterone-Derived Progestins May Be Less Harmful
- Carcinogenic to Breast
- Net Effect Uncertain
 - No Powerful Definitive Study on Total Mortality
 - Effect on Heart May Ultimately Determine Net Effect

my as well.

During the late 1970s and early 1980s, there were serious attempts by epidemiologists to evaluate some of the other possible health risks and benefits associated with unopposed ERT. By the mid-1980s, there was clear evidence that ERT substantially reduces the risk of dying from ischemic heart disease. At that time it was widely believed that this benefit was derived from the favorable effects of ERT on lipid profiles – substantially raising HDL cholesterol and substantially lowering LDL cholesterol – but it now appears likely that other mechanisms are involved as well.

Epidemiologists had also demonstrated unequivocally that ERT could minimize bone loss in the perimenopause and early postmenopausal periods, and that this reduction in bone loss translated into a substantial reduction in risk of osteoporotic fractures, especially those of the hip. Beginning around this time, epidemiologists also began serious efforts to clarify the relationship between ERT and breast cancer risk. A few years ago, a group at Oxford led by Dr. Valerie Beral gathered the raw data from the 51 studies (involving over 160,000 women) published on this possible relationship up until that time.¹ They concluded that there exists a modest, duration-related increase in risk of breast cancer with use of ERT; risk increases of about 10% to 15% after five years of use. They further concluded that the impact of ERT on breast cancer risk was particularly pronounced among thin women. Furthermore, risk dissipated relative to non-hormone users after discontinuing therapy, although the level of risk appears not to return to baseline; i.e., to the level of a lifetime non-ERT user.

Given the rather substantial epidemiologic and experimental evidence for a role of estrogens in breast cancer etiology, it is perhaps surprising that the level of breast cancer risk associated with ERT is so modest, and that establishing this association has proven so difficult. Evidence for a role of estrogens in breast cancer has been previously reviewed by many others.² This evidence includes multiple types of animal models of mammary cancer inducible by estrogens; consistently observed higher estrogen levels in women who develop breast cancer than in compa-

table women who don't; higher estrogen levels in women at high risk of breast cancer such as U.S. whites than in lower risk women such as Japanese and Chinese native to those countries; the stimulatory effects of estrogen on breast epithelial cell proliferation; the proven efficacy of anti-estrogens in breast cancer prevention; and a series of highly reproducible epidemiologic breast cancer risk factors implicating estrogens in breast cancer development (early age at menarche, late age at menopause, high postmenopausal body weight, low physical activity levels, and absence of long-term lactation).

Pike and colleagues have suggested that this relatively modest impact of ERT on breast cancer risk might be related to differences in the degree to which various

Table 2
Risk of Breast Cancer Per Five Years of Use of HRT, ERT, and CHRT Study

	HRT	ERT	CHRT
Magnesson et al., 1999	20%	15%	35%
Schairer et al., 2000		5%	40%
Ross et al., 2000	11%	7%	29%

estrogens can stimulate breast tissue.³ Most epidemiologic data on the relationship between ERT and breast cancer is based on the complex mix of estrogens in Premarin®, which is derived from pregnant mares. Although the precise estrogen composition is unpublished, oral administration of this drug increases circulating levels of many estrogens. However, the level of the most potent estrogen fraction to human breast tissue, estradiol, is approximately doubled in women taking 0.625 mg Premarin® daily, over that of a typical postmenopausal woman using no HRT. As breast cancer incidence increases with age by about 2% per year postmenopausally, doubling the level of estradiol as occurs with ERT use would, according to Pike et al., reasonably result in a further increase in breast cancer incidence of 2% per year. This is almost precisely what has been observed in the Collaborative Group analysis.

In the mid-1980s, we published a paper warning that the addition of progestin to ERT might have substantial adverse effects on the overall risk-benefit

equation for ERT (summarized in Table 1).⁴ We were concerned especially that progestins have the opposite effect of estrogens on lipid profiles and other possible estrogen-mediated cardioprotective effects and that, as a result, a substantial fraction of the cardioprotection provided by ERT might be lost. This concern remains over a decade later, as there has yet to be published a definitive study on the relationship between CHRT and cardiovascular disease incidence and mortality.

We also expressed concerns that the schedule that was being most commonly used for prescribing CHRT, i.e., an unopposed estrogen for the first part of a monthly cycle with the progestin added for approximately the final 10 days, might still result in some residual excess endometrial cancer risk over baseline, due to the stimulatory effect of the unopposed estrogen through the majority of the cycle. We subsequently showed, in the largest and most definitive study of CHRT and endometrial cancer risk conducted to date, that CHRT given as sequential therapy with the progestin added for at least 10 days per month or given as continuous combined therapy (estrogen and progestin delivered

together for the entire cycle) reduces endometrial cancer risk to baseline (i.e., to that of a non-user of HRT) although not beyond. Progestin given for any fewer than 10 days per month resulted in some residual excess of endometrial cancer risk.

Another major concern expressed in that early paper was that the addition of a progestin to ERT might enhance any ERT-related increase in breast cancer risk. Although we believed there were a number of reasons to be concerned about this issue, the primary reason was that progestins appear to enhance cell proliferation in breast tissue substantially above that induced by estrogen alone. The best evidence for this is that mitotic activity in breast epithelium occurs at only a modest level during the follicular phase of a normal menstrual cycle when estrogen is the sole stimulant, but increases to a much higher level in the mid-luteal phase when there is maximum progesterone stimulation.⁵ There is a clear relationship between cell proliferation and malignant transformation.⁶

Despite this concern published many years ago, until earlier this year there

were virtually no published data on the relationship between CHRT and breast cancer risk. The Collaborative Group analysis from Oxford, which included the raw data from the 51 published studies on HRT and breast cancer by 1997, included only 58 breast cancer patients and 86 control women across all of these studies who had used CHRT for at least five years.¹ Nonetheless, despite its very low statistical power, this analysis suggested that the risk associated with CHRT might be at least 50% greater than that of ERT alone.

Three papers published in the past year have provided a more detailed evaluation of this question and more precise estimates of breast cancer risk associated with use of CHRT.⁷⁻⁹ The publication by our group in the *Journal of the National Cancer Institute*⁵ had the most long-term users of CHRT among these three studies. This study included HRT usage histories from nearly 2,600 breast cancer patients over age 55 diagnosed in Los Angeles County, California during the period 1989 to 1996, and identical information from comparable women of the same age, race, and socioeconomic status as the patients themselves. Risk of breast cancer among women who had used any form of HRT was modestly increased with increasing duration of use, so that for each five years of use of HRT, breast cancer risk was increased by 11%. Although modest in magnitude, because of the substantial size of the study, this effect was statistically significant. Risk associated with HRT as unopposed ERT was even lower, so that for each five years of use, risk was estimated to increase by only 7%. Despite large numbers of users, this small increase in risk did not quite achieve statistical significance. For use of HRT as CHRT, risk was increased much more substantially, so that per five years of use risk increased 29% (i.e., more than four times that of ERT), an effect that was highly statistically significant. The other two recently published papers suggested that the impact of CHRT compared to ERT might be even greater than we reported (Table 2), although both of these other data sets were smaller than ours, making their risk estimates somewhat less precise.

Two major concerns in analyzing data on HRT and breast cancer risk are assuring that age at menopause, a potentially powerful confounding variable, has been appropriately dealt with, and that any association between HRT and breast can-

cer is not simply a function of more frequent contact with the health care system (especially more frequent screening by mammography) among women who use HRT. Age at menopause is strongly related to both breast cancer risk and likelihood of being prescribed HRT. Failure to fully adjust for differences in age at menopause between breast cancer patients and controls will tend to overestimate HRT use in controls relative to cases and underestimate the strength of the true relationship between HRT and breast cancer risk. Determination of age at menopause presents a particularly difficult challenge in women who have undergone a simple hysterectomy without removal of the ovaries. We have done extensive evaluations on the impact of various strategies of assigning age at menopause to such women on the relationship between HRT and breast cancer risk, and have concluded that excluding such women from any statistical analyses of this question is the only sensible approach.¹⁰ We think our handling of the age at menopause “problem” was more thorough than any other study published to date on HRT and breast cancer.

We also carefully considered in our study the issue of whether more careful screening for breast cancer in HRT users might explain the observed association, i.e., that the association is an artifact of breast cancers with little or no potential to invade and spread being picked up differentially in HRT users. We accounted for possible differences in the frequency of mammographic screening in breast cancer patients and controls, and this adjustment had no measurable impact on the relationship between CHRT and breast cancer. We also evaluated the relationship between CHRT and breast cancer by stage of breast cancer at the time of diagnosis,

with the expectation that if the association of CHRT with breast cancer was an artifact, risk would be largely or entirely confined to early stage, perhaps especially in situ disease. In fact, the relationship was stronger with somewhat more advanced disease at presentation.

The other issue that we tried to address in our paper was whether the two main schedule strategies for prescribing CHRT (as continuous combined therapy or as sequential therapy) result in differential risk of breast cancer. In our study we found that risk was substantially higher for sequential than for continuous combined therapy (45% increase in risk per five years of use vs. 12%, respectively). We reasoned that this difference might be due to a need for estrogen “priming” of breast epithelium in order to achieve the maximum impact of progestins on cell division in the breast or, alternatively, to the tendency to use lower daily doses of progestin with continuous combined treatment. However, the only other paper to evaluate this question to date did not find lower risk with continuous combined therapy, so this issue must currently be considered unresolved.⁹

While the epidemiologic evidence that progestins substantially enhance the effect of ERT alone on breast cancer risk is compelling, other recent lines of evidence are also highly supportive of this possibility. For example, the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial found that mammographic densities, a strong predictor of breast cancer risk, are increased modestly in women assigned ERT, but are increased substantially in women assigned CHRT.¹¹ Importantly, the PEPI study included both continuous combined and sequential CHRT regimens, and the difference in mammographic density patterns between these two arms was negligible.

“Most of the published data from the United States on CHRT and breast cancer risk relates to medroxyprogesterone acetate, which has suggested to some clinicians that other progestins might prove less harmful to the breast.”

A recent study by Hofseth et al on the impact of various regimens of HRT on cell proliferation indices in breast tissue supports conclusions on cell proliferation patterns in normal cycling premenopausal women.¹² This study evaluated healthy tissue in women undergoing biopsy for breast lesions who were using various HRT regimens. They found mitotic activity was modestly increased in women using ERT vs. no HRT, but substantially increased in women taking CHRT.

There remain other important, not fully answered questions on the relationship between CHRT and breast cancer risk. As noted above, it has been well established that the impact of ERT on breast cancer risk is more substantial in thin women than heavier women, presumably because thin women postmenopausally have lower baseline endogenous estrogen levels than heavier women. One study has suggested this differential effect might also apply to CHRT,⁸ although there is no obvious biologic basis for such a difference. In fact, that study was very poorly powered statistically to detect any differences in risk, so this issue must await larger studies with substantially larger numbers of CHRT users before being resolved conclusively. There are other subgroups of women of special interest with regard to CHRT use and breast cancer risk. For example, it has been suggested that prolonged use of oral contraceptives in women carrying a mutation of one of the high penetrance breast cancer susceptibility genes, BRCA1 and BRCA2, might enhance penetrance further or lower age at onset of breast cancer.¹³ If true, one must wonder if CHRT use might be particularly harmful in women with a family history of breast cancer.

Finally, one study has raised the issue as to whether any association between CHRT and breast cancer risk might be more pronounced for distinct biologic subtypes of breast cancer. Again, one rather poorly statistically powered study has suggested that the impact of CHRT on breast cancer risk might be stronger for lobular than for the more common ductal carcinoma subtype.¹⁴ Final resolution of this issue must also await larger, more definitive studies. Whether CHRT might preferentially induce estrogen receptor and/or progesterone receptor positive tumors is a biologically sensible and

important question, as these tumors would be expected to have a somewhat more favorable prognosis compared to receptor negative tumors. No definitive data are yet available on this possibility.

There can now be little argument in favor of using a progestin as part of HRT in women at no risk of endometrial cancer. It is also now clear that the development of a better delivery system for progestin therapy postmenopausally must be an extremely high public health priority. What is needed is a delivery system that maximizes exposure to the endometrium by the progestin, but minimizes exposure to all other organs. One such delivery system, a progesterone-containing intrauterine device, already exists, but suffers from the inconvenience of periodic insertion, the distinct possibility of periodic bleeding, and the dangers incurred by the increased fragility of the uterine wall postmenopausally. An alternative delivery system using a more convenient, safer, and easier to administer vaginal insert is being preliminarily evaluated at our medical center.

As we continue the development of such a system, alternative strategies to minimize progestin exposure to other organ systems should be considered in the meantime. Less regular administration of progestin (i.e., for example, every three to four months instead of every month as part of CHRT) has been suggested as one possible strategy for accomplishing this goal. In theory, this strategy should result in periodic sloughing of the cells which have undergone initial transformation into a carcinogenic phenotype by virtue of the unopposed estrogen stimulation in the intervening months. There are, in fact, some data to suggest that this strategy will achieve the desired endometrial protection,¹⁵ with the

added benefit of reduced progestin exposure to the heart, brain, breast, and any other organ system adversely affected by progestins.

Most of the published data from the

United States on CHRT and breast cancer risk relates to medroxyprogesterone acetate, which has suggested to some clinicians that other progestins might prove less harmful to the breast. However, as noted above, data on cell proliferation related to natural progesterone are not reassuring, and data from European studies suggest that testosterone-derived progestins are likely to be at least as harmful.⁹ The burden of proof must now shift away from challenging epidemiologists to prove that each new generation progestin causes breast cancer, to challenging the advocates of using such agents to prove that they do not.

The significance of these recent studies on

CHRT and breast cancer is several-fold. These studies, first of all, provide important new data on the role of progestins, at least in combination with estrogen, on breast cancer development. Secondly, these studies provide women and their physicians with important new information to include in their decision making as to whether to start HRT use, and to determine the best formulation and schedule of HRT to meet their needs. Finally, these studies clearly change the balance point for the benefit-to-risk ratio for CHRT. Although final determination of the precise balance point for the benefit to risk ratio of CHRT rests on the still unresolved impact on heart disease risk, it is clear that a firmer understanding of the relationship between CHRT and breast cancer has moved that balance point to a substantially less favorable point than previously thought, and importantly, to a less favorable point than for ERT

“Finally, one study has raised the issue as to whether any association between CHRT and breast cancer risk might be more pronounced for distinct biologic subtypes of breast cancer.”

alone in the majority of postmenopausal women.

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Menopause Management: Tibolone

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INTRODUCTION

Women present to their physicians at the time of diminishing ovarian function with the acute symptoms of estrogen deficiency, the most common of which are vasomotor and/or urogenital symptoms. Other symptoms include mood swings, memory loss, joint pains, and loss of libido. Hormone replacement therapy (HRT) will alleviate many of these symptoms and will prevent long-term effects of ovarian failure. HRT will prevent bone loss, and there is now accumulating evidence that HRT may also decrease the incidence of Alzheimer's disease and protect against colorectal cancer. The evidence for protection against cardiovascular disease is currently controversial.

Despite the short and long-term benefits of HRT, adherence to date has been poor. One of the main reasons for this is that postmenopausal women do not want to have vaginal bleeding. There are now various regimes for non-bleeding hormone replacement therapy including continuous combined therapies composed of estrogen and progestogen, estrogen replacement therapy and a progestogen intrauterine system, selective estrogen receptive modulators, and tibolone, the topic of this article.

PHARMACOLOGY

Tibolone is a synthetic steroid that has estrogenic, progestogenic, and androgenic properties. Structurally it is related to 19 norethisterone derivatives such as norethynodrel and norethisterone. Tibolone has different hormonal activities at different sites. After oral ingestion, tibolone is metabolized predominantly to three other steroid molecules: delta 4 isomer; 3 alpha hydroxy metabolite; and 3 beta hydroxy metabolite. This conversion may occur at the target tissues; hence the concept of tissue specificity. At the level

of the endometrium, the delta 4 isomer predominates and has a progestogenic effect. Therefore the endometrium becomes atrophic. As there is no stimulation of the endometrium, there is no need for the regular withdrawal bleeding associated with conventional HRT.

SYMPTOM RELIEF

Tibolone has been shown to alleviate hot flushes¹ and to be associated with improved mood.² The effect on urogenital symptoms is clearly beneficial.³ Any research into the biology of sexual behavior is complicated for two reasons: (1) sexual behavior involves motivational behavior (testosterone related), and the biological response and the interplay between these two factors are complex; (2) if one aspect of the biological response can be improved, then this may have a knock-on effect on other symptoms; i.e., improving vaginal dryness will decrease dyspareunia which will improve sexual enjoyment (the domino effect).

With tibolone there is an estrogenic effect on the vagina demonstrated by vaginal cytology⁴ which correlates with the subjective improvement in vaginal dryness, dyspareunia, sexual interest, and sexual satisfaction. Androgen replacement therapy has been shown to increase libido and energy levels in postmenopausal women. Therefore, tibolone's androgenic activity may improve the libido independently. Tibolone has been compared to a continuous combined hormone replacement therapy by using the Swedish version of McCoy's sex scale questionnaire which showed that both compounds had a positive effect on sexual life, but tibolone was superior with regard to sexual enjoyment and frequency.⁵

EFFECT ON THE ENDOMETRIUM

Although tibolone does not stimulate the endometrium, some women may experience breakthrough bleeding, most commonly in the first six months of therapy. The women who bleed tend to be younger, recently postmenopausal, and have endogenous estrogen production.⁴ With the advent of transvaginal scanning,

endometrial outpatient samplers, and outpatient hysteroscopy, the assessment of postmenopausal bleeding is much easier. If breakthrough bleeding occurs in the first six months and the woman does not have any significant risk factors, then it is reasonable to reassure her and review after six months. Any bleeding after six months should be investigated as postmenopausal bleeding and managed appropriately.

EFFECT ON THE FEMALE SKELETON

Tibolone protects the postmenopausal skeleton from bone loss³ and this is sustained with long-term use (Rymer – unpublished data). Other groups have shown protection of the skeleton in women with established osteoporosis.^{6,7} In older women, a lower dose of 1.25 mg has also been shown to be bone protective.⁸ In all of these bone studies, adherence

with tibolone has been high (greater than 70%) over the first two years. The biochemical data indicates that the effect of tibolone on bone is to inhibit bone resorption, leading to suppression of the bone formation markers which reflects an overall reduction in bone remodeling.

CARDIOVASCULAR DISEASE

The relationship between the increased incidence of cardiovascular disease and ovarian failure is complex. It was originally thought to be a simple relationship with the change in lipid levels producing an atherogenic profile. However there are many other independent cardiovascular markers that are important, as well as the direct effects of estrogen on the blood

vessels, blood flow, and glucose metabolism. Tibolone causes a decrease in total triglycerides, total cholesterol, and HDL cholesterol, but LDL is unaffected.

Although the decrease in HDL may be interpreted as detrimental, the more

important factor is the function of HDL in the vessel walls. What is needed are long-term studies with focused endpoints.

Unfortunately the issue of HRT protecting against cardiovascular disease remains controversial. We await the results of randomised double-blind placebo-controlled trials investigating HRT and primary prevention and secondary prevention.

THROMBOEMBOLIC DISEASE

Women on HRT have an increased incidence of venous thromboembolism. This may be interpreted as a beneficial effect, although at this stage the relationship between HRT and VTE is unclear. It may be that HRT unmasks a previ-

ously concealed thrombophilia. Tibolone increases fibrinolysis with unchanged coagulation.⁹

Women on HRT are concerned about the effect on the breast tissue. Breast tenderness is one of the most common side-effects of HRT. Tibolone does not appear to cause significant breast pain and has been directly compared to continuous combined therapy.¹⁰ Increased breast density has been shown to have a positive correlation with breast malignancy, and increased density per se makes a diagnosis of breast cancer more difficult. Tibolone does not appear to increase breast density as much as conventional HRT.¹⁰

We do not have the perfectly designed study to answer the question: "Does HRT

“Tibolone has been shown to alleviate hot flushes¹ and to be associated with improved mood.² The effect on urogenital symptoms is clearly beneficial.³”

increase the incidence of breast cancer?" However in 1997,¹¹ the *Lancet* published a meta-analysis of the best studies available. This did show an increased incidence of breast cancer with hormone replacement therapy (duration dependent), but compared to the background incidence for the 50- to 70-year-old age group, the increase in the incidence was small. Also, the tumors that developed in the group on HRT did not appear to be as aggressive. Tibolone does not appear to stimulate the breast tissue, and animal work has shown that tibolone may actually decrease the tumor load and have a tamoxifen like effect.¹² Thus tibolone appears to act as an anti-estrogen on the breast.

SIDE-EFFECTS

As with all forms of HRT, women may experience side-effects in the first few months. But if they persist longer than this, the symptoms should settle down when all the hormonal receptors are saturated. As tibolone has an androgenic profile, a small percentage of women may notice an increase in hair growth, but this has to be set against the other androgenic effects of increased libido and energy. The most common side-effect of tibolone is break-through bleeding, which occurs in 10% to 20% of women depending on age, time since menopause, and any spontaneous bursts of activity.⁴ This compared favorably with rates quoted for continuous combined preparations which were in the range of 25% to 50%.¹³

CLINICAL ADVANTAGES OF TIBOLONE

As tibolone appears to have less estrogenic side-effects than conventional HRT, it is ideal for the postmenopausal woman, particularly if she has not been exposed to estrogen for sometime. If the aim of administering tibolone in a certain woman is for protection of osteoporosis, then the lower dose of 1.25 mg is appropriate, theoretically. Women who have had a hysterectomy in the past for endometriosis would have less chance of reactivation of any remaining endometriosis if they were to take tibolone

rather than estrogen replacement therapy.

In younger women, the use of GnRH analogues is increasing, but they should not be given alone for more than three months because of the significant bone loss that can occur. Tibolone can be used as addback therapy (to prevent bone loss and alleviate hot flushes) in conjunction with the GnRH analogues,¹⁴ allowing women to benefit from the GnRH analogues longer term.

Traditionally, one hesitates to give HRT to women who have had hormone dependent tumors, acknowledging that there is a chance of tumor recurrence. With the in vivo and in vitro animal work on tibolone, the suggestion is that due to its anti-estrogen and tamoxifen-like effects on breast cells, it may be an option for women who have had hormone dependent tumors. There is no human work to date to support this.

SUMMARY

Tibolone appears to be well tolerated, with the major side-effect being break-through bleeding within the first six months in women who still have a uterus. After six months, the vast majority of women will be bleed free; hence adherence rates are high.

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