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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

SEXUALITY AFTER BREAST CANCER



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INTRODUCTION

Female sexual identity, sexual function, and sexual relationships may be dramatically wounded, physically and emotionally, by the many changes and challenges a woman faces when breast cancer diagnosis and treatment (BCD&T) disrupt her life and that of her relatives.¹ Studies, both retrospective² and prospective,³⁻⁷ have been conducted on the many psychosocial issues the woman faces in this difficult transition in her life. This paper will focus on the most important biological factors that may impair sexuality after breast cancer.

FEMALE SEXUAL IDENTITY

Femininity, maternity, eroticism, and social roles all contribute to the perception of female sexual identity and may be variably affected by BCD&T. Femininity may suffer as a result of four distinct biological factors. The first factor is the type of treatment provided. The breast is a prominent personal and social sign of femininity. Body image is the parameter most affected by the type of surgery performed.^{2,4-8} Short-term impact depends on the type of surgery performed (lumpectomy versus mastectomy, with immediate or delayed reconstruction, and the cosmetic result) and whether or not adjuvant radio-

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therapy or chemotherapy is needed. Other more conservative treatment does not appear to significantly modify quality of life (QOL) or female sexuality in the long-term.^{2,5-7}

Secondly, arm lymphedema, although still underdiagnosed and undertreated,^{9,10} may affect femininity, with an average reported incidence of 30% to 40%.^{9,10} Disfigured body image and altered self-perception may lessen the inner sense of femininity, leading to depression and avoidant coping strategies. "Arm problems" were noted by 43% to 72% of the patients in one study based on the different arm symptoms (pain, pins and needles, numbness, skin sensitivity, swelling)⁵ and by 26% to 36% in another.⁶

Iatrogenic menopause is the third biological factor that may decrease the sense of femininity. Younger patients (25% of breast cancer patients are premenopausal) are generally more vulnerable to the complex impact of BCD&T^{2,4,5,11-13} because of the disease itself and the increased risk of a premature menopause induced by chemotherapy; more so as sex hormones modulate the quality of brain aging with its cognitive and emotional symptoms^{14,15} and the quality of aging of sensory organs that are sexual targets and determinants of libido.¹⁶

FROM THE EDITOR

David F. Archer, M.D.

Dr. Alessandra Graziotti returns to *Menopausal Medicine* to discuss female sexuality after diagnosis and treatment of breast cancer. Women are being diagnosed with breast cancer at a younger age, and with improved survival the issues of self-perception, psychological reaction, and interpersonal activities assume greater importance relative to the quality of life. All health care providers should counsel and initiate appropriate treatment for women regarding these interpersonal issues concurrent with and subsequent to breast cancer diagnosis and therapy.

Drs. Janet Guthrie and Lorraine Dennerstein provide the observational and scientific background to address common concerns of women in their mid-life years: weight gain, fatigue, and generalized aches and pains. Consumers want a quick fix for these problems, and obviously hormonal therapy does not provide this. The data are not consistent regarding increased body weight and hormones. It is difficult to motivate consumers regarding the need for long-term behavioral changes, but the realization that these complaints are not related to a decline in estrogen helps in their education.

Drs. Susan Reed, Noel Weiss, and Serene Srouji address the issue of progestin replacement in women with a uterus who are receiving estrogen. Progestins inhibit the development of endometrial hyperplasia and cancer. The introduction of new treatment regimens such as cyclic for 10 or more days, continuous, and pulsed, along with long cycle (every three months) present the physician with a need to evaluate the most effective therapy for their patients. The route, dose, and duration of the progestin can be significant for preventing endometrial cancer.

Menopausal Medicine

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Age is the fourth biological factor that may modify the outcome of BCD&T. Its effect is not limited to the potential impact of the menopause but to the different individual goals of a woman's reproductive years. Maternity may become the core of a major identity crisis for the 25% diagnosed during the fertile age.¹⁷ The most relevant biological issues are discussed in the review of Collichio et al.¹⁸ Conception should be delayed for at least two years after breast cancer treatment, as recurrence risk is highest in this time period; fertility is variably reduced by chemotherapy; the risk of congenital abnormalities following chemotherapy fortunately does not seem to exceed normal incidence;¹⁷ and milk production is reduced in the irradiated breast. The key question patients ask about pregnancy after breast cancer is: "Does pregnancy increase the risk of BC recurrence?" A number of studies deny such risk.¹⁹⁻²³ However, Guinee and coworkers²⁴ have demonstrated a detrimental effect of pregnancy on subclinical breast cancer. Effects of the antiestrogen tamoxifen on human pregnancies have not been reported so far.

Surgery of the breast due to BC may affect sensuality, sexiness, and receptiveness of breast eroticism. Forty-four percent of women with a partial mastectomy and 83% of those with breast reconstruction ($p < 0.001$) report that pleasure with breast caresses had decreased.²

Menopausal symptoms (hot flashes, sweating, mood swings, insomnia, depression, loss of libido, arousal difficulties, orgasmic difficulties, and dyspareunia), physical signs (wrinkles, weight gain, modified body shape, mouth dryness, vaginal dryness, and overall worsened sexual response), and quality of life impairment secondary to iatrogenic (chemotherapeutic) and/or non-hormonally treatable natural menopause may dramatically lessen a woman's sense of eroticism.¹⁰⁻¹³ Women who received chemotherapy tended to desire sexual relations less frequently ($p < 0.032$), had more vaginal dryness ($p < 0.001$) and dyspareunia ($p < 0.001$), had intercourse less frequently ($p < 0.013$), and experienced a reduced ability to reach orgasm through intercourse ($p < 0.043$), although their ability to reach orgasm through non-coital caressing did not differ from that of other women.

Coital receptiveness is therefore selectively damaged. Overall sexual satisfaction

was significantly poorer ($p < 0.001$).²

Depression and anxiety, reactions to BC that may affect self-perception and sexual function via non-hormonal pathways, are reported in approximately 17% to 25% of BC patients.²⁵

The social role may represent an area relatively unaffected by BC, particularly in well-educated women,^{26,27} except in the acute phase or in the more severe and aggressive cases. A strong and positive social role may reduce the impact of BC on other dimensions of femininity, especially in the peri- and postmenopausal years.^{5,27,28} However, 20% of BC survivors report a reduction in energy, with an increase in psychological distress and cognitive problems (difficulties in concentrating, remembering, and thinking clearly).⁵ Cognitive deficits after postoperative adjuvant chemotherapy for BC have been described in a broad range of functions including attention, mental flexibility, speed of processing information, visual memory, and motor function.²⁹ This cognitive impairment is unaffected by anxiety, depression, fatigue, and time since treatment, and is not related to the self-reported complaints of cognitive dysfunction.²⁹

In summary, female sexual identity may be variably affected by BCD&T according to a number of biological factors: age at diagnosis; stage and correlated extension and type of treatment; type and cosmetic outcome of surgery; presence of lymphedema; accomplishment or not of childbearing before diagnosis; infertility; and induction of a premature menopause, including its signs and symptoms. The differentiation of the relative weight of these factors with respect to psychosocial variables deserves further prospective, more biologically oriented studies.

FEMALE SEXUALFUNCTION

Linear models (arousal, plateau, orgasm, resolution) have been used widely since the pioneering work of Masters et al.³⁰ More recently, Graziottin¹⁶ suggested that human sexual function can be considered as a circuit with four main stations: libido, arousal, orgasm, and satisfaction, that includes both the physical phase of resolution, with its homeostatic function of returning to baseline, and the emotional evaluation of the experience.

LIBIDO

Libido has three major dimensions: bio-

logical, motivational-affective, and cognitive^{16,31} that have a complex interplay with both inhibiting or enhancing roles.

Biological roots of libido depend first on sexual hormones, which are necessary but not sufficient factors in maintaining a satisfying human libido.³² They seem to control the intensity of libidinous and sexual behavior, rather than its direction.³¹ After BCD&T, loss of estrogens secondary to iatrogenic or naturally occurring menopause may contribute to inhibiting the sexual drive and physical receptiveness; loss of androgens³³ secondary to chemotherapy or ovariectomy may lessen this drive and receptiveness even further. Sensory organs' involution after menopause may further reduce the biological basis of libido.³⁴ Loss of libido is a multifaceted problem that may be secondary to a number of different factors: arousal disorders due to biological and/or psychological causes;^{11,34} orgasmic disorders;¹¹ and sexual dissatisfaction (physical, emotional, or both). BCD&T may contribute to a complex sexual dysfunction, overlapping in different dimensions of the sexual response.

Motivational-affective and cognitive aspects of libido may be impaired by the negative impact breast surgery has on self-image, self-esteem, and the perception of being an object of sexual desire. The shift in a couple's relationship toward more effective dynamics may increase emotional intimacy but reduce sexual drive. The role of partner rejection secondary to perceived loss of femininity may also be an issue.

SEXUAL AROUSAL

Sexual arousal indicates a state with specific feelings, usually directed toward the genitals.³⁵ In women, arousal difficulties may be central, non-genital peripheral, or genital.³⁶ Breast cancer survivors may suffer from complex arousal disorders, secondary to biological central difficulties caused by the loss of sexual hormones, or due to iatrogenic or spontaneous menopause. Arousal may be worsened by depression, anxiety, chronic stress, and insomnia triggered by the cancer diagnosis. Reduced frequency of erotic dreams, fantasies, sexual daydreams, and spontaneous mental arousal are the clinical consequences of central arousal difficulties reported in BC patients. Problems in non-genital peripheral arousal may be better exemplified by "touch-impaired" disor-

ders.³⁷ Nipple erection may be reduced both by decreased breast sensitivity, secondary to surgery, and by inhibition due to the shame some women feel in exposing the affected breast.

Genital arousal is mediated by the action of Vaso Intestinal Peptide (VIP), the most important neurotransmitter that "translates" sexual drive into vaginal lubrication.³⁶ Without estrogen, 35% to 45% of normal postmenopausal women complain of vaginal dryness and dyspareunia.^{13,37,38} Pre-existing arousal disorders may be further worsened by the menopausal loss of estrogens and loss of libido many women complain of after breast cancer. A second biological cause of arousal difficulties is the defensive spasm of the pubococcygeal muscle, secondary to vaginal dryness and dyspareunia.³⁹ The attention to hypertonic conditions of the pelvic floor secondary to dyspareunia is mandatory in BC patients, as teaching relaxation of the levator ani muscle and encouraging self-massage with medicated oil may rapidly cure dyspareunia and arousal disorders secondary to hypoestrogenism that may not be treatable with estrogens because of BC. Vascular problems have recently been claimed as critical factors in female arousal problems.⁴⁰ Women who smoke and/or have high levels of cholesterol with diabetic vasculopathy, and/or those with severe atherosclerosis, may have a significant reduction in their genital arousal with reduced lubrication, vaginal dryness, and dyspareunia. BC patients with consistently good libido but with vascular arousal disorders might have significant clinical improvement with vasoactive drugs such as sildenafil,⁴¹ which would not be contraindicated in BC patients. Studies of sildenafil have been controversial so far. Considering the high prevalence of dyspareunia in BC patients, the possibility that this non-hormonal drug may be helpful deserves to be evaluated further.

Overall, in the prospective longitudinal study of Ganz and coworkers,⁵ difficulty in becoming sexually aroused was reported by 61% of BC patients, while difficulty in becoming lubricated was reported by 57% of patients. Interestingly, Ganz et al found that BC survivors attain maximum recovery from the physical and psychological trauma of cancer treatment within one year after surgery. Many aspects of quality of life (QOL), rehabilitation (mainly arm problems), and sexuality sig-

nificantly worsen after that time, suggesting that some biological factors might be responsible for this trend. According to the retrospective study of Schover et al,² BC women who received chemotherapy reported more vaginal dryness ($P<0.001$) and dyspareunia ($P<0.001$). Overall, postmenopausal BC women (either with natural or chemotherapeutic menopause) were more likely to report vaginal dryness and tightness with sexual activity ($P<0.001$) and genital pain with sexual activity ($P=0.004$).

ORGASM

Orgasmic difficulties may be the end point of many biological, motivational-affective, and cognitive factors. In BC patients, difficulty in reaching orgasm was reported in 55% of patients in the prospective longitudinal study of Ganz et al,⁵ with a significant worsening in sexual functioning during the three-year follow-up. In the Schover et al retrospective study,² the ability to reach orgasm through intercourse tended to be reduced significantly in women who received chemotherapy ($P=0.043$), although their ability to reach orgasm through non-coital caressing did not differ from control women. Inhibitory effect of dyspareunia on vaginal orgasm might explain this difference, together with the effect of different dominant neurochemical pathways (Nitric Oxide (NO) androgen dependent, for clitoral response; Vaso Intestinal Peptide (VIP), estrogen dependent, for the vaginal response.)³⁶

SATISFACTION

Satisfaction is a comprehensive yet elusive word. It includes both physical and emotional satisfaction that should probably be investigated as separate parameters. Pain and an overall disappointing sexual experience might also be responsible for the significantly reduced satisfaction ($P<0.001$) reported by BC survivors in the retrospective study of Schover et al² and in the prospective study of Dorval et al⁶ who report a significantly reduced satisfaction ($P<0.003$) in BC survivors eight years after primary treatment, in comparison to age-matched controls.

Objective parameters used to quantify and qualify sexual satisfaction, both at physical and the emotional levels, are still to be defined. This methodological problem is to be overcome before data on BC

survivors' sexual satisfaction may be understood in their full meaning.

SEXUAL RELATIONSHIP

Quality of affective relationships, specifically of sexual relationships (both homosexual and heterosexual), is a critical part of human adult satisfaction. Good quality emotional intimacy may explain why 62% of BC patients found it easier to discuss their sexual problems with their partners during their illness than with doctors and psychologists, to whom only 15% of BC patients openly expressed their concerns.³⁴

Cancer diagnosis is a tremendous strain on the couple's relationship and family unit.^{1,42} Younger women and couples may be particularly vulnerable. Studies indicate that younger women experience more emotional distress than older women.⁴³ Younger husbands reported more problems carrying out domestic roles ($P < 0.001$) and more vulnerability to the number of life stressors they were experiencing ($p < 0.01$) in comparison to older husbands. When BC is diagnosed, the demands of the illness are superimposed on the normal demands of family life, and this may have a different impact on family relationships, depending on the phase of the family life cycle when the cancer is diagnosed.⁴⁴

Focusing on the physical aspect of the problem, breast surgery may affect physical attractiveness and reduce comfort with breast foreplay, although this is difficult for patients to admit as it seems insensitive and/or unfeeling. Loss of estrogen may also make vaginal penetration more difficult because of vaginal dryness.¹¹⁻¹³ It could also precipitate an erectile deficit, when dryness itself challenges the quality of the erection or when the partner perceives vaginal dryness as a sign of refusal or an indication of the "insensitivity" of his sexual request. This loss of estrogen may lead to impairment of male physical and emotional satisfaction, when the instinctual drive is impeded by physical difficulties and emotional concerns. Couples express relief and gratefulness when these issues are raised by the physician during the consultation and when practical suggestions are given to overcome physical and emotional problems.

HORMONE REPLACEMENT THERAPY

Breast cancer is still considered a contraindication to HRT. However, it may be

considered in individual cases when the subjective impact of the menopause is dramatically disruptive to the woman's quality of life. The physician should have a detailed discussion with the woman concerning the benefits and risks, including the lack of definitive evidence in favor of HRT and the lack of substantial negative effects of HRT after breast cancer.

CONCLUSIONS

Breast cancer may affect female sexual function, female sexual response, and the couple relationship in a complex way, involving both psychosocial and biological factors so closely interrelated that it is difficult to determine the relative weight of hormonal and overall physical changes on psychosexual variations in BC survivors.

Physicians, particularly oncologists in this field, should improve their skills in understanding and listening to sexual concerns and in addressing the basic biological issues that BC raises for female sexual identity. They should diagnose and recommend clinical help for the most common sexual symptoms in BC survivors: loss of libido, arousal disorders, dyspareunia, anorgasmia, and loss of satisfaction. After the physician has excluded or treated the potential biological roots of the problem, patients with clear psychodynamic or relational problems should be referred to a psychosexologist or psychiatrist specializing in this field. This sharing of a "twin competence" will yield the best results. Additionally, in order to give BC survivors a complete diagnosis and competent help, attention to pelvic floor anatomy and function should be made part of a thorough clinical gynecological and sexological examination.

Finally, approximately 70% to 80% of BC survivors experience a positive overall psychological adjustment and quality of life. However, this is not true of sexual functioning and satisfaction.^{2,4-7,34} An understanding and competent physician can help the woman and the couple to better cope with the strain of breast cancer without giving up sexual intimacy, which is a critical part of quality of life.

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Weight Gain, Somatic Symptoms, and the Menopause



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INTRODUCTION

Middle-aged women often complain to their physicians about weight gain and a variety of other symptoms. An important clinical question which needs to be determined about these complaints is whether they relate to menopausal hormonal changes or to aging, other health states, psychosocial factors, or lifestyle.¹ Conflicting findings reported in the literature about the etiology of symptoms in mid-life reflect some of the methodological difficulties in menopause research, such as cross-sectional design, sample selection, and separation of the effects of natural menopause from that of induced menopause. In order to distinguish menopause-related symptoms from those of aging, it is necessary to study women as they experience the natural transition from pre- to postmenopause in population-based cohorts. Changes also occur in body composition during the mid-life years. There is an increase in weight and a change in fat distribution. Recent evidence about body composition changes and symptom reporting during the menopausal transition is summarized below.

WEIGHT AND FAT DISTRIBUTION Importance of Weight Gain and Changes in Fat Distribution

Cardiovascular diseases are the leading cause of death among women in the United States. The risk of coronary heart disease (CHD) in women rises with increasing relative body weight (body mass

index), increasing age, increased cigarette smoking, and decreased exercise. In a prospective study of middle-aged women, the factor which had the most influence on cardiovascular risk was high body mass index (BMI).² High BMI is associated with elevated serum lipids, lipoproteins, and blood pressure; these also contribute to an elevated risk of CHD. An increase in intra-abdominal adipose tissue is well-known as a risk factor for several metabolic complications including hyperinsulinemia, insulin resistance, and dyslipidemia. These complications are associated with the development of type 2 diabetes, which is a strong independent risk factor for CHD³ as well as for ischemic stroke and total cardiovascular mortality among middle-aged women.⁴

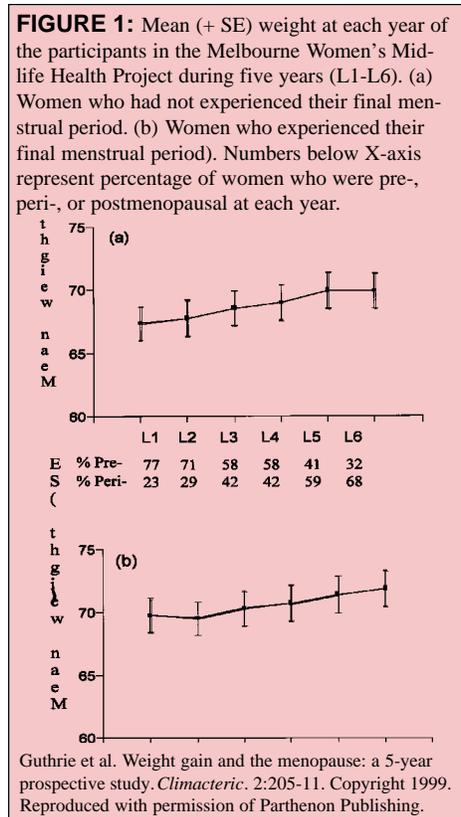
Mid-Life Weight Gain

Women tend to gain weight and increase their central body fatness in mid-life.^{5,6} To promote the prevention of excess weight gain and alterations in fat distribution during the mid-life years, we need to know the pattern of these changes and any reasons for its occurrence.

Information about changes in body weight and composition have come mainly from cross-sectional studies.⁶⁻¹³ Data from these studies suggest that BMI is increased in peri- and postmenopausal women compared with premenopausal women,^{6,7} and that there is an increase in fat mass and a change in body fat distribution.⁶⁻¹³ Several studies reported that these changes were associated with the menopause,^{7,11,13} while others found a dependence on chronological age,⁸⁻¹² or years since menopause and age,⁶ or associations with age of menarche and parity independent of menopausal status.¹¹ Prospective studies have reported a weight increase in middle-aged women not associated with the menopause^{5,14-16} or with age of menarche.¹⁴ There is also controversy as to whether hormone replacement therapy prevents mid-life weight gain and an android shift in body fat distribution.^{9,12,14,17-19}

In prospective studies, the mean weight gained has varied depending on the population studied. A mean weight gain of 2.0 kg over five years of follow-up during the menopausal transition was reported in a population-based cohort of Australian-born women living in Melbourne¹⁶ aged 45 to 55 at baseline. This was similar to an American population of the same age

range, but their study was over a three-year follow-up period.⁵ These studies permitted a comparison of age-related changes versus those attributable to the natural menopausal transition. In both studies, there was no significant difference in weight gain in women who remained premenopausal and those who experienced a natural menopause. Figures 1a and 1b illustrate the mean weight of the cohort at each year of follow-up in the Australian study of mid-life women who had (1b) and had not (1a) experienced their final menstrual period during this time.



In a cross-sectional study of a population-based cohort (n=728), there was a negative correlation between exercise levels and BMI.²⁰ In longitudinal studies, the findings between exercise and weight gain have varied. Some authors report no association between change in exercise and change in weight,¹⁶ while others⁵ report a significant association between decreases in exercise and increases in body weight. This may reflect a difference in the populations or in the types of physical activity questionnaires used to assess exercise levels. Where there was an association, the increase in exercise was recorded as an increase in intensity rather than frequency.

Mechanisms responsible for weight increase in middle-aged women are unclear. Pasquali⁷ reported that in a study

of 596 women (aged 42 to 60 years), energy intake tended to be higher in the perimenopausal group compared to the other groups but found no association between exercise and weight changes. There is a reported decline in lean mass around the time of the menopause,²¹ and this may be responsible for a significant reduction in resting metabolic rate and decrease in energy expenditure during physical activity in postmenopausal women. The magnitude of the decline in resting metabolic rate during the menopausal transition has been estimated to be responsible for an increase in body fat of 3-4 kg.²²

An increase in body weight is a result of energy intake exceeding energy expenditure. Body weight will rise until the energy expenditure associated with the elevated weight is equal to energy intake, at which point body weight stabilizes.²³ If there is a decrease in daily energy expenditure, as suggested above, and no change in energy input, then body fat gain will occur during this period of positive energy imbalance. The most variable component of daily energy expenditure is the thermic effect of physical activity.²² Even small changes in the level of physical activity over an extensive period of time could have important implications in the regulation of body weight during mid-life. In summary, if middle-aged women maintain their level of physical activity but do not reduce their calorie intake, weight gain will occur.

Researchers from the University of Pittsburgh, USA reported an average 2 kg weight gain over three years, from a longitudinal study of 541 women during the menopausal transition (The Healthy Women's Study).⁵ Further reports from this study²⁴ indicate that by eight years postmenopause, these women had gained an average of 5.5 kg, and one of the most clinically significant predictors of this weight gain was decreased physical activity.

Can Lifestyle Interventions Help?

In a follow-up of the Healthy Women's Study, a five-year randomized clinical trial was conducted to see whether a dietary and physical activity lifestyle intervention could prevent the rise in body weight and other cardiovascular risk factors during the pre- to postmenopause period.²⁴ The lifestyle intervention included a dietary goal to consume 25% or less total calories from fat, and a physical activity program of brisk walking, 10

to 15 miles per week. After six and 18 months of treatment, the lifestyle intervention group had significant reductions in weight and other cardiovascular risk factors compared with the control group. At 54 months, the intervention group had a very small mean loss of weight compared with a mean 2.4 kg gain in the control group. Also, a significant reduction of 2.9 cm in waist circumference was found for the lifestyle intervention group, compared with a reduction of 0.46 cm in the control group. While further work is needed to see if these lifestyle interventions can be maintained over a longer period and whether they are effective in other ethnic groups, it has succeeded in preventing weight gain and reducing waist circumference during a high-risk period of weight gain, and could have a major impact on reducing cardiovascular morbidity and mortality in the long-term.

Does Hormone Replacement Therapy Prevent Weight Gain?

In the Australian observational study,¹⁶ women who remained on hormone replacement therapy (HRT) throughout a five-year period did not experience a change in their mean weight. However, only a small number of women comprised this group (n=21) and it is not possible to claim that the data provide confirmatory evidence that HRT prevents weight gain in mid-life women. Excessive weight gain has been reported as a side effect of HRT,²⁵ although in most controlled trials women using HRT showed a reduced weight gain or no difference compared with controls.¹⁷⁻¹⁹ It is possible that results from these studies reflect that women with a high compliance for HRT are women who are unlikely to gain weight in this mid-life period. Whether HRT protects against weight gain may also depend on the age at which women start hormone treatment.

Is the Change in Fat Distribution Related to the Menopause?

Body fat distribution can be estimated using a number of different methods. The most commonly used anthropometric index is the waist-to-hip ratio (WHR); others have used waist circumference, skin-fold measures, dual energy X-ray absorptiometry (DEXA) measures of truncular fat, and computed tomography of intra-abdominal adipose tissue. In cross-sectional studies,²¹ significant effects of

the menopause, independent of age, were noted when techniques such as DEXA or computed tomography were used. These precise techniques led to the conclusion that the menopause transition accelerates the increase in intra-abdominal fat. WHR or waist circumference failed to detect significant effects of the menopause in other cross-sectional studies, but did so in longitudinal studies.²¹ Results of six- and five-year follow-up studies^{14,26} which compared women who changed their menopausal status from pre- to post-menopause with women who remained premenopausal found that the menopause transition was associated with an accelerated increase in central adiposity. The BMI changes were identical in the two groups. Central fat accumulation was recorded by measuring waist circumference, waist-to-hip ratio, and supra-iliac skin-fold measurement. Poehlman and colleagues²⁶ also reported that women who experienced the menopause transition had significantly greater increases in total fat mass, measured by hydrostatic weighing, compared with women who remained premenopausal.

Why Does Fat Distribution Change?

Sex hormones have been implicated in menopause-associated changes in body fatness and body fat distribution. Estradiol levels decrease rapidly around the time of the final menstrual period²⁷ and there is an increase in the free androgen index (FAI).²⁸ Mean testosterone levels do not vary with time relative to the final menstrual period but there is a decrease in sex hormone-binding globulin (SHBG) due, at least partially, to the decline in estradiol levels.²⁸ SHBG levels also decrease with increasing BMI²⁸ so mid-life weight gain will have an effect on SHBG and subsequently FAI levels. Adrenal androgens such as dehydroepiandrosterone sulfate (DHEAS) decrease as a function of age, but not time relative to the final menstrual period.

However, the factors that influence the distribution of body fat are not really known. The changing levels of estrogens, free androgens, and SHBG during the menopausal transition may act directly on fat stores or they may modify expression of genes controlling adipocyte differentiation and metabolism. In normal ovulating women, basal lipoprotein lipase (LPL) activity is higher in subcutaneous femoral adipose tissue than in abdominal sites,

and this femoral adipose tissue may serve the specialized function of providing a readily utilized fat store in the reproductive years. Femoral fat cells are larger than abdominal fat cells, a difference attributed to high femoral fat LPL activity. However, after menopause, femoral adipocytes lose their higher LPL activity²⁹ and abdominal LPL activity does not change. This could explain a shift of adipose accumulation toward the abdominal area. Hormone replacement therapy has been reported in some studies^{17,18} to attenuate the menopause related acceleration of central fat accumulation and has also been shown to stimulate LPL activity in the femoral region.³⁰ This suggests that estrogen deficiency may directly influence regional adipose tissue metabolism.

More studies are needed to determine the factors that influence the distribution of body fat. In particular, studies need to look at the influence of hormones on genes associated with adipocyte differentiation and metabolism, measure longitudinal changes in fat distribution using DEXA, and relate these to hormone changes.

MID-LIFE SYMPTOMS REPORTED Methodology

A major issue in the recording of symptoms is the validity and reliability of the symptom measure. The standard method used for collecting information on the prevalence and severity of symptoms has been a checklist of symptoms, but this introduces the problem of elicitation, with more positive responses to a checklist than to open-ended questions. When frequency or severity of complaints is included, prevalence of reported symptoms is typically reduced. Another methodologic issue in epidemiologic studies is the lack of longitudinal studies that use hormone measures and short follow-up. Below we summarize results from the Melbourne Women's Midlife Health Project (MWMHP) that used a number of strategies to overcome these problems in study design. This project was a longitudinal study of a population-based sample of women aged 45 to 55 who were followed for seven years from baseline. The women were asked annually about frequency and severity of bothersome symptoms (from a 32-item check-list) in the previous two weeks to minimize recall bias. Annual blood samples were collected for measuring hormone levels, and annual data on menstrual status were re-

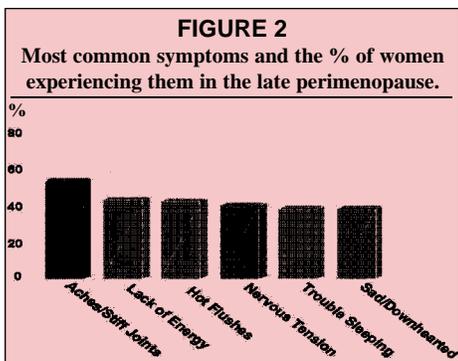
corded to determine the phase of natural menopause.³¹ These phases of the menopausal transition were defined as premenopausal if they reported no change in frequency of menses, early perimenopausal if there were changes in frequency of their menses, late perimenopausal if they reported amenorrhoea of at least three but less than 12 months, and naturally postmenopausal if there was amenorrhoea for 12 or more consecutive months.³²

Menopausal Transition Symptoms

The proportion of women in the MWMHP who reported a particular symptom as bothersome in the previous two weeks for each category of the menopause is given in Table 1. By postmenopause, almost all women were reporting at least one symptom and most were reporting five or

Phase of Menopausal Transition	None	One	Five or more
Premenopause (n=172)	6	13	40
Early Perimenopause (n=148)	4	13	42
Late Perimenopause (n=106)	5	11	56
Postmenopause 1 year (n=72)	1	11	51
Postmenopause 2 years (n=54)	0	9	56
Postmenopause 3 years (n=31)	0	10	52

more. The number of women who reported five or more symptoms increased by 14% between early and late perimenopause. Figure 2 illustrates the most common symptoms reported and the proportion of women reporting these symptoms.



Symptom severity scores over the pre- and early perimenopausal years were compared with those over the late perimenopausal and postmenopausal years.³¹ The only symptoms which registered significant increases were hot flashes, night sweats, vaginal dryness, and trouble sleeping. There was also a significant decrease in breast soreness. The symptom of trouble sleeping followed a more gradual increase across the menopausal categories and appeared to relate both to aging and the

hormonal changes of the menopause.

Longitudinal population-based studies are best able to establish likely relationships between symptoms and physical, psychosocial, and lifestyle factors. The MWMHP was one of few longitudinal population-based studies to include hormone levels and found that estradiol was the best predictor for vasomotor symptoms. The development of hot flushes in the late perimenopause was increased for lower levels of estradiol. Length of smoking (in pack-years) contributed to the reporting of hot flushes. Vaginal dryness increased exponentially with time from the late perimenopause, indicating that it was a later consequence of hormonal changes during menopause. Women with tertiary education were less likely to report this symptom, suggesting that increased knowledge might be related to factors that helped women with maintaining sexual function. Trouble sleeping was related both to hot flush reporting and depression.

Other Somatic Symptoms

During the seven-year study period of the MWMHP, one of the most common symptoms reported was aching or stiff joints, this being a problem in approximately 50% of the participants. There was little change in the prevalence of these symptoms over the study period and it was not significantly associated with menopausal status. Also, arthritis was the most common chronic condition, being reported at some stage during the study about 50% of the participants. Though bone and joint pain has been reported as a feature of the menopause,³³ there are few studies that specifically address this issue. Further studies are needed to clarify whether these problems are an effect of age, are menopause-related, are associated with current or past lifestyle habits, or are most likely a combination of all these factors.

CONCLUSIONS

In conclusion, there is a change in weight and fat distribution in our cohort during the mid-life years. It is most likely that a combination of hormonal and non-hormonal factors contribute to weight increases and changes in fat distribution. The menopause transition may be a period of change in energy regulation. There is a decrease in lean mass and an increase in fat mass and a decrease in energy expenditure. The reduction in lipoprotein lipase activity in femoral adipose tissue, combined with

decreased energy expenditure, may lead to the increased accumulation of intra-abdominal adipose tissue. This central adiposity is most strongly correlated with insulin resistance and cardiovascular risk. Dietary and exercise interventions are to be encouraged. Using prospective population-based research, we found that symptoms directly related to the hormonal changes during the menopausal transition were vasomotor symptoms, atrophic vaginal problems, and breast tenderness. Insomnia was indirectly associated with this hormonal change. These are symptoms most likely to respond to hormonal intervention.

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COMBINED POST-MENOPAUSAL HORMONE THERAPY AND RISK OF ENDOMETRIAL CANCER



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INTRODUCTION

Use of unopposed estrogens by postmenopausal women is associated with a large increase in the risk of endometrial

cancer.¹ The size of the increase correlates with the duration of estrogen use, and the absolute risk can equal or exceed 1% per year in long-term users. It is likely that this adverse influence of estrogens is attributable to the ability of these hormones to stimulate proliferation of endometrial tissue, cellular proliferation being a prerequisite for carcinogenesis.

Estrogen use is efficacious in treating vasomotor and other symptoms that are common in the early postmenopausal years, and over the long-term has a favorable influence on bone density and fracture risk. Following are reasons to believe that, in order to provide long-term estrogen therapy that will not be deleterious to the endometrium, a progestational agent should be added to the regimen:

1. Progesterone secreted by the ovaries of premenopausal women stops endometrial proliferation and stimulates differentiation of endometrial cells;
2. Exogenous progestogens, when taken in conjunction with estrogens in the form of oral contraceptives, generally lead to a reduction in the risk of endometrial cancer.¹ It is noteworthy that the one type of oral contraceptive (Oracon®) usage associated with an increased risk of endometrial cancer contained the weakest progestational agent (dimethisterone) of any formulation in its class;
3. Cessation of unopposed estrogen and the initiation of a continuous high-dose progestogen can lead to regression of endometrial hyperplasia, a precursor of endometrial cancer.²⁻⁴

Our goal here is to review evidence regarding the risk of endometrial cancer in relation to the various means of incorporating a progestogen into a regimen of postmenopausal estrogen therapy.

PROGESTOGEN EFFECTS ON THE DEVELOPMENT OF ENDOMETRIAL HYPERPLASIA

It is widely accepted that endometrial hyperplasia with atypia is a precursor lesion to endometrial cancer, with an estimated 25% progression to cancer without treatment.^{2,5} Review of pathologic specimens from individual women suggests a continuum beginning with simple hyperplasia, progressing to complex hyperplasia, hyperplasia with atypia, and finally to endometrioid type endometrial carcinoma.² Analysis of 146 pathology specimens of endometrial carcinoma showed a high frequency of a spectrum of

hyperplastic changes, ranging from simple hyperplasia to atypical hyperplasia in 15% of the cases.⁶

Furthermore, biochemical markers of both endometrial hyperplasia and endometrial carcinoma suggest an increase in cell turnover indices and cell apoptosis, and increased nuclear expression of oncogenes (Bcl-2, ras, and PTEN)^{7,8} in a progressive fashion, moving from precursor lesions or hyperplasia to carcinoma.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) study⁹ was a three-year randomized controlled trial in which endometrial biopsies were obtained from 596 postmenopausal women. In this large trial, 45% of women taking unopposed estrogen for two years developed endometrial hyperplasia; among women taking unopposed estrogen for three years, the corresponding figure was 62%. Approximately one-third of these were atypical hyperplasias. The expected time course for the development of endometrial hyperplasia in women with a progestogen dose or monthly duration that is insufficient to block its development is unknown, but probably varies widely and may be longer than that expected for unopposed estrogen exposure. Studies analyzing the risk of endometrial hyperplasia in relation to a regimen of combined estrogen-progestogen therapy in postmenopausal women are predominantly of 12 months' duration. We therefore need to be cautious in interpreting the results of such trials as a guide to the impact of a given regimen on the later risk of endometrial cancer. Only eight out of 24 prospective randomized clinical studies on the effects of the addition of progestogen to postmenopausal estrogen therapy followed women for 24 months or longer;⁹⁻¹² these are summarized in Table 1.

IMPACT OF DIFFERENT REGIMENS OF COMBINATION HORMONE THERAPY ON ENDOMETRIAL HYPERPLASIA AND CANCER RISK

How important is monthly duration and pattern of progestogen use? The results of epidemiologic studies to date permit two firm conclusions:

1. In terms of a postmenopausal woman's risk of endometrial cancer, taking a progestogen along with an estrogen preparation is safer than taking the estrogen alone;¹³⁻¹⁵
2. The full magnitude of the benefit

afforded by use of progestogen is not obtained unless that hormone is taken for at least 10 days each month.¹³⁻¹⁵

Unfortunately, from these same studies it is not yet possible to answer the following important questions:

1. Relative to the risk of endometrial cancer among women who have not used hormones, what is the risk associated with long-term use of combined estrogen/progestogen therapy in which the progestogen is taken for at least 10 days each month?
2. Does the risk differ depending on whether the progestogen is taken cyclically for 10 to 14 days per month or every day?
3. What is the effect of a regimen given in a pulsed fashion, three days on, three days off?
4. Can a cyclic regimen be taken quarterly, allowing women several months without any progestogen? A summary of the evidence bearing on these questions follows.

Monthly Cyclic Regimens

Among estrogen users, the incidence of endometrial hyperplasia is greater in women who take a progestogen for fewer than 10 days each month than in women who take it for 10 or more days.^{16,17} In the two case-control studies that were able to examine this question,^{13,14} the same pattern emerged with about a two-fold greater incidence of endometrial cancer in women who took the progestogen for fewer than 10 days per month.

Because the benefits of hormone therapy (e.g., to the skeleton) diminish rapidly once hormone use ceases, many postmenopausal women are prescribed hormones for a number of years. Observational epidemiologic studies of endometrial cancer in relation to long-term (e.g., five or more years) use of combined hormone therapy are particularly relevant, given that it is particularly with long-term use of unopposed estrogens that the incidence of endometrial cancer is elevated. Trials examining the development of endometrial hyperplasia in women assigned at random to estrogen use and combined therapy have dealt with no more than the first several years of use. Unfortunately, the results of these studies are not in agreement with one another. Investigators in Seattle¹⁴ and Sweden¹⁵ have reported that women who have taken cyclically combined therapy for five or more years have two to three times the risk of endometrial cancer as women who have not taken hormones. In contrast,

every day. Because the latter (combined-continuous) therapy has been in common use for a relatively short time, a comparison of its impact on risk of endometrial cancer, relative to the impact of cyclic therapy, has had to account for differential duration of use. When this was done in the Seattle and Swedish studies,^{15,18} there was a several-fold lower risk associated with combined-continuous therapy. In fact, in both studies the risk in women taking this therapy was lower than that of hormone nonusers. However, a study in Los Angeles¹³ observed no difference in risk between women taking cyclic or combined-continuous regimens. In another study, 38 women who had been taking cyclically combined therapy and had evidence of endometrial hyperplasia were switched to a combined-continuous regimen, and after nine months all had reverted to a normal endometrium.¹⁹ While this observation is compatible with a true beneficial influence of combined-continuous

therapy on the endometrium, the absence of a comparable group with hyperplasia in whom cyclic therapy was continued (or all hormone treatment stopped) hinders its interpretation.

Long cycle combined therapy (cyclical progestogen given every third month)
Progestogen therapy causes side effects

Author Year Setting	Estrogen			Progestin			Number Biopsied at Study Completion	
	Type	Daily Dose (mg)	Days per month	Type	Daily Dose (mg)	Days per month		
CYCLICAL								
Clisham ¹⁰ 1992 UCLA	1. TE 2. TE	0.1 0.1	1-24.5 1-24.5	None MPA	--- 10	--- 13-25	30 30	20 26
CYCLICAL Long cycle								
Heikkinen ¹¹ 1997 Finland	1. Placebo 2. EV 3. EV	2 2	1-21 1-84	MPA MPA	10 20	12-21 71-84	(78 total)	(76 total)
Bjarnason 1996 Scandinavia Multicenter	1. 17BE 2. 17BE	2 2 1 2 1	1-68 69-78 79-84 1-22 23-28	--- NETA --- NETA ---	--- 1.0 --- 1.0 ---	--- 69-78 --- 13-22 ---	120 120	(145 total)
CONTINUOUS								
Bryjalsen ²⁰ 1992 Denmark	1. Placebo 2. EV 3. 17BE	--- 2 1.5	--- 1-21 1-24	--- MPA DSG	--- 10 0.15	--- 12-21 13-24	23 25 25	18 18 20
CHART ³⁵ 1996 US Multicenter	1. Placebo 2. EE 3. EE 4. EE 5. EE 6. EE 7. EE 8. EE 9. EE	--- 0.001 0.0025 0.005 0.010 0.001 0.0025 0.005 0.010	--- 1-28 1-28 1-28 1-28 1-28 1-28 1-28 1-28 1-28	--- NETA NETA NETA NETA None None None None	--- 0.2 0.5 1.0 1.0 --- --- --- --- ---	--- 1-28 1-28 1-28 1-28 --- --- --- --- ---	137 139 136 146 145 141 137 141 143	59 69 57 65 65 64 67 90 18
CYCLICAL & CONTINUOUS								
Obe ¹¹ 1993 Denmark	1. Placebo 2. 17BE 3. 17BE	--- 2 1 2	--- 1-22 23-28 1-28	--- NETA --- NETA	--- 1 --- 1	--- 13-22 --- 1-28	51 50 50	42 19 42
PEPI ⁹ 1996 U.S. Multicenter	1. Placebo 2. CE 3. CE 4. CE 5. CE	--- 0.625 0.625 0.625 0.625	--- 1-28 1-28 1-28 1-28	--- None MPA MPA MP	--- --- 10 2.5 200	--- --- 1-12 1-28 1-12	119 119 118 120 120	102 98 108 109 110
Heikkinen ¹² 2000 Finland	1. EV 2. EV 3. EV 4. EV 5. EV 6. EV	1-2* 1-2* 2 2 1 1	1-28 1-28 1-28 1-28 1-28 1-28	MPA MPA MPA MPA MPA MPA	2.5 5.0 2.5 5.0 2.5 5.0	1-28 1-28 1-28 1-28 1-28 1-28	70 70 70 70 69 70	61 61 42 61 63 61
TE=transdermal estrogen; MPA=medroxyprogesterone acetate; EV=estradiol valerate; 17BE=17β estradiol; NETA=norethindrone acetate; DSG=desogestrel; EE=ethinyl estradiol; CE=conjugated estrogen; MP=micronized progesterone								
*estradiol valerate was given at 1 mg per day in study months 0-6 and 2 mg per day in study months 7-24.								

investigators in Los Angeles¹³ observed no difference in risk. Conceivably, this heterogeneity could be due to the nature of the study populations regarding their prior use of unopposed estrogens.¹⁷ In contrast to the participants in the Los Angeles study, Seattle women who had previously taken estrogens alone were excluded from all analyses, and in Swe-

den the large majority of users of combined hormone therapy had not previously taken estrogens alone.

Combined-Continuous Regimens

The incidence of endometrial hyperplasia is low both in women who have received cyclic progestogen (e.g., 10-14 days per month) and in those who have received it

including abdominal bloating, mastalgia, and mood disturbances. These side effects, in conjunction with cyclical bleeding experienced with sequential therapy, lessen compliance with hormone replacement therapy. To maximize compliance, regimens with less frequent progestogen dosing have been used.

A trial to assess the impact of 10 days of progestogen given quarterly was conducted on 240 postmenopausal Scandinavian women.²⁰ The women were randomized to an 84-day cycle or a 28-day cycle of daily 17 β -estradiol, 2 mg per day, and 10 days of norethindrone acetate, 1 mg per day. The study followed these women up to four years and found that the overall prevalence of hyperplasia in annual endometrial biopsies was higher in the long cycle group, 12.5%, versus 2.5% in the short cycle group. In the long cycle group, five cases (4.2%) of complex hyperplasia, one case (0.8%) of complex hyperplasia with atypia, and one case (0.8%) of a well-differentiated endometrioid carcinoma occurred during the entire study period, as compared to only two cases (1.7%) of complex hyperplasia in the monthly cycle group.

Though other studies have monitored the experience of women on long cycle therapy, none of these studies were randomized trials.^{11,12,21,22} For example, Ettinger and colleagues followed postmenopausal women for one year on 13-week cycles of conjugated estrogen with 14 days of medroxyprogesterone acetate. Three (1.5%) cases of endometrial hyperplasia were identified in the 199 women who completed the follow-up.²¹ Kemp et al followed 85 women for four years, cycling them on six months of oral conjugated estrogen and norethisterone for 10 days with a seven-day drug-free period. Only 51 participants had annual endometrial biopsies taken over two years, and two cases of atypical adenomatous hyperplasia were diagnosed.²²

In summary, though the impact of long cycle regimens on the endometrium has not been studied extensively, there is a suggestion that it may be less favorable than the effect of regimens that include the use of a progestational agent for at least 10 days every month.

Pulsed progestogen (three days on, three days off)

Because it takes a few days for unopposed estrogen to up-regulate endometrial

estrogen receptors, and because several days of exposure to a progestogen results in down-regulation of the estrogen receptor, it has been proposed that an intermittent pulsed progestogen dosing regimen of three days on and three days off would be as beneficial to the endometrium as continuous progestogen. In theory, the pulsed progestogen would result in fewer side effects because of a lower total monthly progestogen dose.²³

In a 12-month double-blind trial, 1,253 postmenopausal women were randomized to estrogen only (1 mg of 17 β -estradiol) or to estrogen of the same dose with one of three pulsed progestogen regimens (norgestimate 0.03 mg, 0.09 mg, or 0.18 mg), given three days on and three days off.²⁴ There were no women with hyperplasia in the two highest progestogen regimens (0.09 and 0.18 mg) containing 242 and 243 women, respectively. In the lowest dose progestogen group (0.03 mg) with 260 women, there were two with either complex or atypical hyperplasia (<1%) and 14 (5.4%) with simple hyperplasia. In the comparison group of 265 women taking unopposed estrogen, there were 74 women with hyperplasia (28%), 10 of whom had complex or atypical hyperplasia (3.8%).

The results of this large trial suggest that pulsed progestogen at higher doses (at least 0.09 mg of norgestimate) may afford a relatively lower monthly dose of progestogen without the development of undue endometrial proliferation. Studies of women receiving this regimen who are followed for longer periods of time are warranted.

DOES ROUTE OF ADMINISTRATION MATTER?

Progestogens have been administered sublingually, intranasally, vaginally, orally, by intramuscular injection, via rectal suppository, transdermally by patches and gels, and via implants and IUD reservoir systems. Oral and transdermal patch administrations are the only routes with Food and Drug Administration (FDA) approval for hormone therapy in postmenopausal women.

Transdermal patch

Among women prescribed transdermal norethindrone, 0.25 mg per day, average serum concentrations of norethindrone were 0.84 ng/ml. This serum concentration was approximately one-third that of

women taking an oral preparation of 1 mg per day of norethindrone.²⁵ Nonetheless, two 12-month studies (as yet unpublished) suggest that transdermal norethindrone acetate 0.14 or 0.25 mg, given in continuous or cyclic fashion with estradiol, 0.05 mg, was associated with the same low risk of endometrial hyperplasia as orally administered progestogen.²⁵

Vaginal Gel

Currently available vaginal or rectal progesterone products are not approved for postmenopausal use, and twice daily administration by these routes would seem to be inconvenient and not acceptable to many women. Women who use 45 mg of progesterone vaginal gel every other day have higher levels of serum progesterone than women taking the same oral dose.²⁶ Measurement of tissue levels of progesterone after vaginal administration suggest selective uptake by the uterus.²⁷ In 31 postmenopausal women receiving either 45 mg or 90 mg of progesterone gel every other day over 12 days of the month, no instances of hyperplasia were observed over a three-month period.²⁸

Intrauterine Progestogen

Intrauterine progesterone therapy via an intrauterine device has been proposed as another alternative to avoid the systemic side effects of progestogens. In women receiving intrauterine progesterone, local endometrial tissue concentrations of levonorgestrel are sufficient to exert inhibitory effects on endometrial proliferation while serum concentrations remain relatively low.^{29,30}

Anderson et al randomized 40 women with climacteric complaints to receive a sequential regimen of 2 mg estradiol with 10 days of 0.25 mg levonorgestrel each month, or continuous estradiol with a 0.020 mg per 24-hour levonorgestrel-releasing intrauterine device (LNG-IUD). Results at one year revealed no evidence of hyperplasia among women in either group.³¹ A study performed by Suvanto-Luukkonen et al³² involved only 12 women using a percutaneous estradiol gel and 0.020 mg per 24 hour LNG-IUD. After five years, no cases of hyperplasia were identified. Intrauterine progesterone will need to be used by considerably more women, and for longer durations, before any firm conclusions regarding its safety can be reached.

SHOULD THE TYPE OF PROGESTOGEN BE A CONSIDERATION?

Progestogens in clinical use can be broadly classified into four categories and are summarized in Table 2:

1. progesterone itself (micronized in the oral form to improve digestive tract absorption by increasing its surface area)
2. synthetic C-21 progestogens (most common form is medroxyprogesterone acetate);
3. synthetic 19-nortestosterone derivatives – estrane progestins (for example, norethindrone);
4. synthetic 19-nortestosterone derivatives – gonane progestins (for example, levonorgestrel)

Direct comparisons of different types of progestogens and the associated risk of endometrial hyperplasia are reviewed below.

C-21 Progestogen Versus Micronized Progesterone

Due to the rapid inactivation and poor bioavailability of orally administered natural progesterone, synthetic steroids mimicking endogenous progesterone effects were developed in the 1950s. Subsequent research utilizing the micronized form of natural progesterone showed improved absorption and equal efficacy at inducing progesterone-mediated responses.³³

The PEPI trial used 28-day cycles of placebo, estrogen only, or one of three estrogen/progestogen regimens. One of the progestogen regimens included conjugated estrogens with 12 days per month medroxyprogesterone acetate, 10 mg per day; and another included conjugated estrogen with 12 days per month of oral micronized progesterone, 200 mg per day. Six abnormal biopsies (five cases of simple hyperplasia and one case of atypia) (5%) were identified in the micronized progesterone arm, compared to six (four simple hyperplasia and two complex) (5%) in the medroxyprogesterone acetate arm. There were three abnormal biopsies (one case of adenocarcinoma, one simple hyperplasia, and one complex hyperplasia) in the placebo arm (2.5%).⁹

C-21 Versus Nortestosterone-Derived Progestogens

A single European trial has analyzed endometrial cancer risk by type of progestogen (19-nortestosterone derivatives (e.g. norethisterone, norethisterone acetate, levonorgestrel, lynestrenol) and C-21 progestogens (e.g. medroxyproges-

terone acetate).¹⁵ Cyclic regimens with C-21 progestogens were associated with an increase in the risk of endometrial cancer (odds ratio (OR) per year of use 1.12, 95% Confidence Interval (CI) 1.06, 1.18) whereas no association was found with having taken a testosterone-derived progestogen (OR per year of use 1.0, 95% CI 0.95, 1.06). Continuous use of a testosterone-derived progestogen was associated with a reduced risk of endometrial cancer (OR 0.85 per year of use, 95% CI 0.73, 0.98). There were too few women on continuous

C-21 type progestogens to meaningfully assess the influence of this particular regimen on cancer risks.

DAILY PROGESTOGEN DOSE

There are no studies of the dose of oral progestogen, either in cyclical or continuous-combined regimens, in relation to the risk of endometrial cancer. Information from studies of endometrial hyperplasia follows.

Medroxyprogesterone Acetate, Continuous-Combined Regimen

Woodruff and colleagues³⁴ performed a 12-month double-blind, randomized multicenter study in 1,724 postmenopausal women. Two of the five groups were randomized to conjugated estrogen, 0.625 mg daily with either 2.5 or 5.0 mg medroxyprogesterone acetate daily. Three of the 279 women receiving the 2.5 mg dose and none of the 274 women receiving the 5.0 mg dose had endometrial hyperplasia on biopsy at either six or 12 months ($p>0.05$).

Norethindrone Acetate, Continuous-Combined Regimen

The Continuous Hormones as Replace-

Table 2

Brands of products containing progestogen with information on the risk of endometrial hyperplasia in postmenopausal women, grouped by progestogen type

	Brand Names	Available Strength (mg)
Progesterone		
• Micronized progesterone (oral)	Prometrium®	100, 200
• Micronized progesterone (vaginal gel)	Crinone®	45, 90
C-21 Progestogens		
• Medroxyprogesterone acetate (oral)	Provera®	2.5, 5.0, 10
	Cycrin®	2.5, 5.0, 10
	Curretab®	10
	Amen®	10
	Prempro®**	2.5, 5.0
• Cyproterone acetate (oral)*		0.5, 1.0, 2.0
• Megestrol acetate (oral)	Megace®	20, 40
19-Nortestosterone Derivatives (estrans)		
• Norethindrone acetate (oral)	Activella®**	0.5
	Aygestin®	5.0
	Femhrt® **	1.0
• Norethindrone acetate (transdermal)	Combipatch®**	0.14, 0.25
• Norethindrone (oral)	Micronor®	0.35
	Nor-QD®	0.35
19-Nortestosterone Derivatives (gonanes)		
• Norgestimate (oral pulsed)	Ortho-prefest®**	0.09
• dl-Norgestrel (oral)	Ovrette®	0.075
• Levonorgestrel (IUD)	Mirena®	0.02
• Levonorgestrel (oral)*		0.075
• Desogestrel (oral)*		0.15
*Not marketed in the United States ** Also contain estrogen		

ment Trial (CHART)³⁵ is one of the largest randomized controlled dosing trials for postmenopausal combined therapy to date. After 24 months, endometrial hyperplasia developed in one of 69 women (1.4%) randomly assigned to receive a regimen containing 0.2 mg norethindrone acetate and 0.001 mg ethinyl estradiol. No cases of hyperplasia were found in women in three other combined estrogen/progestogen arms of this trial. Endometrial hyperplasia in the four unopposed estrogen arms of the trial was observed in eight out of 221 women (3.6%).

Medroxyprogesterone Acetate, Cyclical Regimen

Woodruff and Pickar³⁴ compared women taking daily conjugated estrogen, 0.625 mg, and either 5.0 mg or 10 mg of medroxyprogesterone acetate, taken for 14 days of the month. Four of the 277 women taking the 5.0 mg cyclical dose and none of the 272 women taking the 10 mg cyclical dose (1.4%) had endometrial hyperplasia on biopsy at six or 12 months ($p>0.05$).

WHAT ADDITIONAL INFORMATION IS NEEDED?

A fair amount of research has been devoted to the safety of at least several regimens currently in widespread use. Nonetheless, several questions about these regimens remain that would readily be addressed by further research:

1. Continuous-combined hormone therapy taken for up to several years appears not to produce an excess risk of endometrial cancer, nor does up to several years of cyclically combined therapy in which the progestogen is taken for at best 10 days per month. However, the safety of longer durations of these regimens – say, beyond five years – needs to be examined further.

2. In those parts of the world where long-term cyclical use of nortestosterone-derived progestogens is common, case-control studies of endometrial cancer could be done to follow-up on the suggestion that regimens that employ these particular agents do not share the modest increase in risk associated with regimens that employ C-21-derived

progestogens.

3. It has been difficult for interview-based case-control studies to assess the impact of the dose of oral progestogen on risk of endometrial cancer, since many women are uncertain about the dose they have taken. Studies conducted in populations served by comprehensive medical care plans that have access to pharmacy records have the potential to overcome this limitation.

For women receiving more recently introduced progestogen regimens, such as pulsed progestogens, transdermal progestins, progestogen-containing IUDs, and micronized progesterone, longer-term follow-up for the occurrence of hyperplasia is needed. Also, to the extent that these localized and/or refined products are used by large numbers of postmenopausal women, case-control studies of endometrial cancer will have the potential to address their impact.

Summary

It is clear that a progestogen adminis-

tered in conjunction with an estrogen preparation reduces the risk of endometrial cancer a postmenopausal woman would have from using estrogen alone. It is equally clear that, at least during the first several years of use, some progestogen regimens achieve this reduction to a greater degree than do others. However, for many promising regimens, the long-term risk of endometrial hyperplasia or cancer is unknown at present, and data relevant to these issues will be awaited eagerly.

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