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FOR CLINICIANS WHO PROVIDE CARE FOR WOMEN

Ovarian Preservation for Women with Malignant Diseases: New Technologies May Be Around the Corner

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INTRODUCTION

Over the past several years there has been an increase in the long-term survival rates of young patients with malignant diseases. Hodgkin's disease is the most common malignancy in the population aged 15 to 24 years, with over 8,000 cases annually within the United States alone. Due to aggressive treatment of Hodgkin's disease with chemotherapy regimens such as MOPP (mechlorethamine, vincristine, procarbazine, prednisone) and ABVD (adriamycin, bleomycin, vinblastine, dacarbazine), prolonged survival rates of over 88% can be achieved.[1,2] Similar statements of high long-term survival rates can also be made about patients with leukemia, non-Hodgkin's lymphoma, breast cancer, and thyroid cancer, as well as for patients with other types of tumors receiving chemotherapy.[3-5] Cytotoxic agents have also been used as chemotherapy for various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and organ transplantation.

These high long-term survival rates come at a high-cost, as treatment is associated with significant morbidity in many patients. The most common long-term side-effect of chemotherapy is an alteration in gonadal function resulting in severe oligospermia or azoospermia in the male and premature ovarian failure in the female.

Ovarian damage from cytotoxic chemotherapy has been shown to be agent, dose, and age dependent, with progressively smaller doses required to induce permanent ovarian failure with increasing age. The chemotherapeutic agents that have the highest gonadal toxicity include alkylating agents (cyclophosphamide, chlorambucil, mustine, melphalan), antimetabolites such as cytarbine, vinca alkaloids and others (procarbazine, cisplatin).[6-10]

Ovarian biopsies after chemotherapy have demonstrated a significant reduction in the number of primordial ovarian follicles after chemotherapy.[11] This reduction in primordial follicles decreases the number of follicles available for follicular recruitment in future cycles, thus decreasing the life span of the ovary. Since older patients have a smaller pool of oocytes prior to chemotherapy, they are more likely to have ovarian failure following therapy.

Radiation therapy can also have a profound impact on ovarian function. Data have been acquired from women treated with pelvic radiation therapy for dysfunctional uterine bleeding or malignancies such as Hodgkin's disease and

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FROM THE EDITOR

David F. Archer, M.D.

Dr. John Schnorr provides us with insight into the ever developing world of reproductive advances. The use of freezing sperm for males undergoing chemotherapy, radiation therapy, or gonadectomy for neoplasia has been with us for many years. We have not had reasonable and convenient methods for women who are undergoing the same therapies for malignancy. In this article the beginnings of the use of cryopreserved and fresh ovarian tissue to maintain hormone levels and provide gametes are explored. These techniques are with us now.

Dr. Margery Gass introduces the reader to the multiplicity of factors involved in compliance with a medication or preventive health strategy. A major issue is the health benefits of continuation vs. intermittent use or discontinuation of a medication. If you have ever had to take medication on a regular basis, you can identify with this article.

Dr. Robert Wild presents the information on both the incidence and the attributal risk of venous thromboembolism with the use of estrogens, and selective estrogen receptor modulators in postmenopausal women. The morbidity and mortality are low. The need to weigh the risk benefit ratio is important in counseling women.

Dr. Robert Lindsay has provided us with a commentary on a recent publication from the HERS trial regarding vertebral fracture in older women on hormone therapy.

Menopausal Medicine

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those treated with total body irradiation prior to bone marrow transplantation. The effect of radiation therapy on ovarian function also appears to be dose and age dependent. Ovarian doses of less than 4 Gy do not typically result in ovarian failure.[12] Women younger than the age of 40 years are less sensitive to radiation-induced ovarian damage, with an estimated dose of 20 Gy required to produce ovarian failure compared to 6 Gy in women greater than 40 years of age.[13]

While younger patients appear to be more resistant to the effects of chemotherapy and radiation therapy, the reduction in the number of primordial follicles from chemotherapy results in a high incidence of premature ovarian failure prior to the age of 30 years.[14] Compared to controls, the relative risk of ovarian failure in young cancer survivors between the ages of 21 to 25 years is 3.7 for those who received radiation therapy alone and 9.2 for those treated with alkylating agents alone.[14] The combination of chemotherapy and radiation therapy commonly administered prior to bone marrow transplantation results in a greater than 90% ovarian failure.[15]

Young women with premature ovarian failure have a deficiency of sex steroids for many years longer than do women undergoing menopause naturally. This premature loss of ovarian function can result in significant psychosocial sequelae with major health implications as demonstrated by a nearly two-fold age-specific increase in mortality rate compared with controls.[16,17] More specifically, a survey of more than 19,000 women ages 25 to 100 years indicates that ovarian failure occurring before 40 years of age is associated with an age-adjusted odds ratio of death due to coronary artery disease of 1.29, stroke 3.07, cancer 1.83, and all other causes being 2.[14,18]

While conventional hormone replacement therapy is a necessity for patients with premature ovarian failure, it is clearly fraught with difficulties. One of the greatest challenges is maintaining compliance, as one-year compliance rates are estimated to be 50% and four-year compliance rates 20%.[19,20] Patients with premature ovarian failure also appear to have a decreased efficacy of hormone replacement at conventional doses, as two-thirds of women with karyotypically normal spontaneous premature ovarian failure have a bone mineral density one standard deviation below the mean of similar aged women despite having taken standard hormone replacement therapy.[21] Androgen replacement should also be considered for women with persistent fatigue, poor well-being, and low libido.

In addition to the loss of sex steroids and its overall impact on physical health, individuals with premature ovarian failure also are faced with a loss of gametes for reproduction and consequently permanent infertility. Patients with premature ovarian failure are candidates for donor egg technologies, but this frequently results in a significant compromise for both the patient and her spouse.

THE USE OF OVARIAN TRANSPOSITION IN PATIENTS UNDERGOING RADIATION

For patients who will only receive pelvic or abdominal radiation therapy, transposition of the ovaries to a site outside of the radiation field is an option. Although ovarian transposition has been shown to reduce the incidence of ovarian dysfunction, the ovaries are exposed to a significant amount of scattered radiation and vascular compromise. As a result, a substantial number of individuals will experience ovarian failure.[22-24] Feeney et al. in 1994 studied the ovarian function in 28 patients who received pelvic radiation therapy for cervical cancer after undergoing ovarian transposition during radical hysterectomies. They found that despite ovarian transposition, 14 of 28 (50%) patients experienced ovarian failure, with a relative risk of 17.3.[25] A similar study with 24 patients who underwent ovarian transposition followed by radiation therapy for cervical cancer resulted in 4 women (17%) with ovarian function after radiation therapy.[26,27]

USE OF OVARIAN SUPRESSION IN PATIENTS UNDERGOING CHEMOTHERAPY/RADIATION

Various hormonal methods have been tried in an attempt to decrease the metabolic rate of the ovary and hence the chemotherapy/radiation therapy gonadal toxicity. Scant data are available regarding oral contraceptives use during chemotherapy. Chapman et al. demonstrated that patients with Hodgkin's lymphoma who received chemotherapy with concurrent oral contraceptives had a higher number of primordial follicles after chemotherapy than those treated without

oral contraceptives.[5,28] Whitehead et al. studied nine women with Hodgkin's lymphoma who underwent chemotherapy (MVPP) with concurrent oral contraceptive administration and found that seven of the nine (78%) developed ovarian failure, thus demonstrating no protective effect from the oral contraceptives.[29]

Gonadotropin-releasing hormone (GnRH) analogue administration prior to chemotherapy has been studied in rodents, non-human primates, and humans with conflicting but encouraging results. GnRH agonist administration causes an initial flare of gonadotropins followed by suppression of gonadotropins and down regulation of the GnRH receptor at the pituitary and perhaps the ovarian level. This leads to atresia of developing follicles as well as inhibition of recruitment of small follicles.

In the Rhesus monkey, two studies have demonstrated that GnRH agonists were ineffective in ameliorating the gonadal toxicity caused by irradiation in both males and females.[30,31] The results are more optimistic regarding GnRH agonist treatment with concurrent alkylating agent administration, as Ataya et al. demonstrated a 30% reduction in the number of primordial follicles with GnRH agonist and cyclophosphamide cotreatment compared with a 65% reduction in the cyclophosphamide group alone.[32]

A prospective clinical trial was conducted by Blumenfeld et al. in 18 cycling women with lymphoma aged 15 to 40 years. Patients were administered a GnRH agonist for six months starting two weeks prior to chemotherapy. Two patients died from refractory disease and 15 of the 16 (93%) remaining patients resumed spontaneous ovulation and menses within three to eight months, compared with seven of 18 (39%) in the retrospective historical control group. Of note, however, only four of 16 (25%) patients in the GnRH treated group received cyclophosphamide compared with 10 out of 18 (56%) in the control group. The median dose of cyclophosphamide was 781 mg/m2 in the GnRH treated group and 2,133 mg/m2 in the control group. Both women (one GnRH treated and one control) who received high-dose chemotherapy and autologous bone marrow transplantation developed premature ovarian failure.[33]

A similar study by Waxman et al. using buserelin, a potent GnRH agonist, in 20 men and eight women with Hodgkin's lymphoma undergoing cytotoxic chemotherapy was conducted. In all patients a GnRH stimulation test was performed one week before and on the first day of each cycle of chemotherapy. All patients' peak luteinizing hormone responses to GnRH stimulation were suppressed throughout treatment. At follow-up assessment up to three years from the completion of treatment, all men treated with Buserelin were profoundly oligospermic and four of the eight (50%) women were amenorrheic, compared with all 10 male controls oligospermic and six of nine (67%) female controls amenorrheic.[34]

THE USE OFART AND OOCYTE CRYOPRESERVATION PRIOR TO CHEMOTHERAPY/ RADIATION

The use of assisted reproductive technologies (ART) prior to chemotherapy can provide additional options to patients. To date, centers around the world have accumulated a large amount of experience with ovarian stimulation with gonadotropins followed by oocyte retrieval and fertilization, which can yield multiple embryos. These embryos can be successfully cryopreserved with a 70% survival rate and high clinical pregnancy rates. This process, even with the use of new GnRH antagonists, can take two to three weeks and requires fertilization with sperm. This approach does not provide restoration of ovarian hormonal production, and frequently the time required for stimulation and need of a male partner are unacceptable.

Cryopreservation of mature, unfertilized oocytes prior to chemotherapy would in theory allow the preservation of female gametes without the necessity for sperm. This process requires ovarian stimulation and on the whole has been less successful than embryo freezing. The most notable exception is the cryopreservation of unfertilized mouse eggs that has resulted in high rates of cryopreservation survival, but success rates rarely match those of embryos.[35,36] Cryopreservation of human, unfertilized oocytes has been more problematic, with difficulties including zona hardening, digyny, and spindle disruption. Porcu et al. have reported on the largest series of unfertilized, mature oocyte freezing in which they have achieved three clinical pregnancies in 23 patients (13%) from 375 oocytes.[37,38]

"Cryopreservation of mature, unfertilized oocytes prior to chemotherapy would in theory allow the preservation of female gametes without the necessity for sperm."

CRYOPRESERVATION OF OVARIAN TISSUE PRIOR TO CHEMOTHERAPY/ RADIATION

A new and rapidly evolving possibility for ovarian preservation in patients who will receive radiation therapy or chemotherapy is the cryopreservation of ovarian tissue. Although this is still in its infancy, ovarian tissue cryopreservation is an attractive alternative, as the ovarian cortex of young women contains several hundred thousand primordial follicles. These follicles are smaller, contain less cytoplasmic fluid, and are surrounded by dense stroma, making them more resistant to the cryopreservation process.

Ovarian tissue cryopreservation has the advantage that slices of ovarian tissue or entire ovaries can be collected by laparoscopy without delaying radiation or chemotherapy treatment. The fresh ovarian tissue can be immediately transplanted in a site out of the field of radiation or, in the case of chemotherapy, the cryopreserved tissue can be transplanted after chemotherapy providing both preservation of gametes and continuous hormonal production. The amount of ovarian tissue needed to restore ovarian function is not currently known. However, ovulation in

women and mice can occur with as few as 100 oocytes.[39]

Gosden et al. conducted numerous ovarian transplantation studies on sheep and demonstrated the successful autologous transplantation of ovarian tissue in both fresh and cryopreserved cycles. After both fresh and cryopreserved ovarian tissue transplantation, the animals had regular menstrual function, cyclic estradiol and progesterone concentrations, and live offspring in two of the animals who underwent transplantation; one pregnancy from fresh tissue and the other from cryopreserved tissue.[40,41]

More recently, Schnorr et al. performed a series of ovarian transplantations in 16 Cynomolgus monkeys at the Jones Institute for Reproductive Medicine. Fresh autologous ovarian tissue was transplanted into the upper arm in six primates, which resulted in restoration of cyclic ovarian function in five of the six primates (83%). Cryopreserved ovarian tissue was transplanted in four primates with restoration of ovarian function in two (50%). Ovarian stimulation of both the fresh and cryopreserved transplanted ovarian tissue resulted in the production and retrieval of mature oocytes.[42]

Human studies have also demonstrated the viability of both fresh and cryopreserved autologous ovarian transplantation. Oktay et al. has reported on two cases of ovarian transplantation. The first case involved a 32-year-old woman who had her ovaries removed for benign reasons. Ovarian tissue was then grafted subcutaneously in the forearm. Ultrasound monitoring four months after the procedures indicated that the grafts are still intact and early antral follicular development has been noted with high frequency ultrasound probes. A gradient was also detected for estradiol between the antecubital vein and the wrist vein indicating hormonal production by the graft.[43]

The second patient also underwent bilateral salpingo-oophorectomy for benign reasons and had her ovarian tissue cryopreserved. The ovarian tissue was cryopreserved for a total of eight months, after which a portion of the ovarian tissue was thawed and laparoscopically transplanted into the ovarian fascia. Four months after the procedure, the 29-year-old patient was noted to have dominant follicle formation with the administration of menopausal gonadotropins and cyclic estradiol and progesterone concentrations.[44]

Many questions still remain regarding the role of ovarian tissue cryopreservation and transplantation. Perhaps the biggest question is its safety. If cancer cells were present in an ovary at the time of collection, then transplantation could establish cancer in the recipient. Accordingly, further research in the field of ovarian tissue cryopreservation is needed to identify ovarian tissue with microscopic metastasis, determine optimum cryopreservation and transplantation protocols, and demonstrate healthy offspring in humans.

Over the past several years, there has been an increase in the long-term survival rates of young patients with malignant diseases. The increased survival rates are due primarily to aggressive modern oncologic therapies including radiation therapy and chemotherapy, which frequently result in a high incidence of ovarian failure. Gynecologists are frequently consulted by referring physicians and patients in an effort to decrease the gonadal toxicity associated with these aggressive therapies. Unfortunately, we often don't have many options to offer. Recent research in the field of ovarian tissue cryopreservation and ovarian transplantation may offer new hope to young cancer survivors.

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HRT Adherence Issues

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INTRODUCTION

The number of women in the United States using hormone replacement therapy (HRT) more than doubled between the years of 1986 and 1992[1] (Figure 1). Of all the pharmaceutical drugs in use in the United States in 1992, Premarin® was the most frequently prescribed brand-name drug. Even outside the United States there has been considerable growth in HRT use. Reports from Sweden, for example, indicate that there was a 7% to 10% use of HRT in the 1980s compared with a 21% to 34% use in 1997, a three-fold increase.[2]

Despite the expansion of HRT use, low continuation rates remain an issue. Various studies have indicated that as many as 20% to 50% of new users stop HRT within 12 months, 10% use it intermittently, and only 30% to 40% can be considered long-term users.[3-6] In one large health plan, less than 20% of women starting HRT were still using it three years later.[7]

HRT ADHERENCE COMPARED TO OTHER DRUGS

The issue of adherence is not unique to HRT. It has long been recognized that as many as 60% of patients do not complete the prescribed course of antibiotics when they are acutely ill.[8] Patients have been known to discontinue antibiotics as soon as they feel better. Long-term use of medication for chronic illness has also been shown to have sporadic compliance. The percent of pills taken ranges from 50% to 90%.[9] Adherence at this level has been found in studies of the chronic use of psychiatric medication as well as in studies of the use of anti-epileptic drugs.[10] With regard to oral contraceptives, it has been reported that only 25% to 37% were able to achieve perfect compliance over a short interval and 51% were found to have missed three or more pills during one cycle.[10]

If we compare the 50% to 90% adherence rates reported for HRT with a drug which might be used in place of HRT, such as a bisphosphonate for osteoporosis, we find a similar rate of adherence. A retrospective study of 812 women who were prescribed alendronate determined that only 54% of the women were still using the drug 10 months later.[11]

ADHERENCE, COMPLIANCE, ACCEPTANCE, CONTINUATION

Adherence terminology is evolving. The widely used term compliance has fallen into disfavor largely because of the connotation of obedience. The general definition of compliance includes conforming to another person's wishes. With greater participation of the patient in the selection of treatment options, the term compliance seems less appropriate overall. Other terms such as adherence and patient acceptance have appeared in the literature. These terms do not differentiate between the different types of adherence. Two important aspects of adherence are: 1) continuing to take the medication, and, 2) taking the medication in the manner prescribed. For the purpose of differentiating between the two in this discussion, the former will be referred to as "continuation rate" and the latter "compliance rate."

FIGURE 1.

ESTIMATED NUMBER OF WOMEN TAKING HORMONE REPLACEMENT THERAPY.[1]

1986	2.9 Million
1992	6.0 Million

Compliance Rate

The importance of taking a medication as prescribed depends upon the medication and the condition for which it is prescribed. Complying with a specific regimen of HRT may be less critical than complying with a coumadin regimen or a digoxin regimen. Poor compliance with a treatment regimen may result in more serious and acute sequelae than poor compliance with a prophylactic regimen. In the older population, 11% of hospital admissions have been attributed to failure to take medications as prescribed.[12] Thus, the degree of compliance required for health benefits may depend on the drug and the circumstances. Taking 75% of the medication prescribed has been the definition of compliance used in some studies. Such a standard may be far too liberal in the case of coumadin or oral contraceptives.

Accurate compliance rates are difficult to obtain. Self-reports are not always accurate, as patients tend to overestimate the number of pills they take. The overestimation found with self-report has been documented in studies where data from computerized pill containers were used concomitantly with self-report to assess compliance. A review of the studies that have used the microelectronic method of monitoring the number of pills taken found that, in general, patients take approximately 75% of the doses in the manner prescribed.[10]

Another method of measuring compliance takes advantage of prescription databases. Comparing the number of pills purchased versus the number of pills prescribed for the year can yield an estimate of compliance. One such study used the definition of compliance described above that required patients to take at least 75% of the pills that had been prescribed for the year. Calculations were based on the number of refills requested. Among 28,718 new users of HRT who were between the ages of 40 and 59, only 46% were found to be compliant at the end of one year.[13]

Continuation Rate

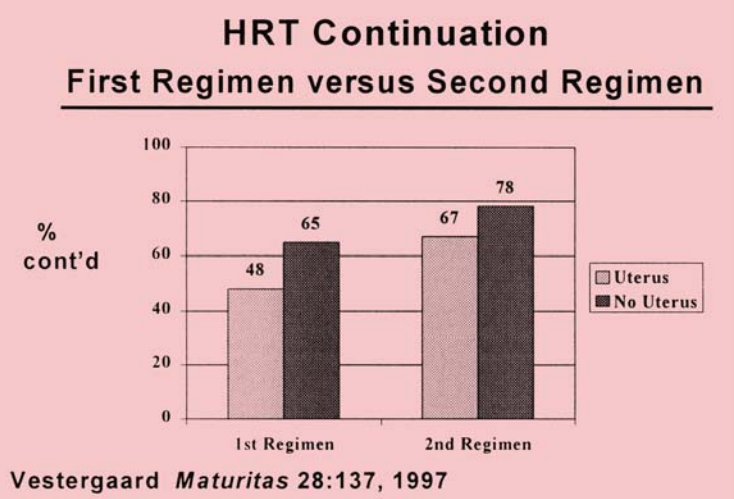
Strict compliance with a specific HRT regimen may not be the most important aspect of adherence. With so many regimens and doses on the market, it is clear that there is no one right way to take

HRT. The less complaint patient may experience some breakthrough bleeding if she skips some of her doses, but overall she is likely to obtain benefits from the medication if she is taking it most of the time. Of greater concern is the large percentage of women who discontinue HRT altogether. These women will not be receiving the long-term benefits. Discontinuation is not a medical problem if women are only seeking relief of the acute symptoms associated with menopause. However, to obtain the long-term health benefits such as prevention of osteoporosis, extended use of HRT is required. The benefits of HRT, such as improved bone density, are not maintained after discontinuation of treatment.

In 1993 a consensus development conference on osteoporosis estimated that no more than one-third of post-menopausal women would elect long-term use of HRT.[14] A review of the literature found that <24% of women with a diagnosis of osteoporosis were using HRT.[5] A collection of studies published in the last five years reported continuation rates of 40% to 68% during the first two years.[3,13,15]

FIGURE 2.

CONTINUATION CAN BE IMPROVED BY SWITCHING TO A SECOND REGIMEN.



FACTORS AFFECTING CONTINUATION RATES

The continuation rate with HRT has been the subject of much scrutiny. Findings from the various reports can be instructive for clinicians concerned about this issue. By knowing which patients are more likely to discontinue HRT, the clinician can recommend more frequent office visits in the first six months to assist the patient in managing her concerns about using hormones.

Symptoms

Menopausal symptoms are the most common motivating factor for initiating HRT.[2] The newly menopausal woman is more likely to seek HRT because of discomfort, whether it be vasomotor symptoms or dyspareunia. The Epidemiologic Followup Study of a cohort derived from the First National Health and Nutrition Survey (NHANES I) found that women who experienced a surgical menopause were more likely to use HRT than women experiencing a natural menopause. In addition the use of HRT by women with a hysterectomy but with ovaries intact was intermediate to the use of HRT by the natural menopause group and by the surgical menopause group.[1] Surgically induced menopause has been cited as a reason for initiating HRT in as many as 35% of current users. In the same study almost half (49.5%) of the women continuing HRT no longer had a uterus.[16] These data suggest that symptoms, such as those found in the surgically menopausal woman, and absence of bleeding such as in the woman with a hysterectomy, are two key factors in the initiation and continuation of HRT.

FIGURE 3.

WOMEN ARE MORE LIKELY TO CONTINUE HRT IF THEY FEEL BETTER ON IT. HRT CONTINUATION ACCORDING TO HOW WOMEN FELT ON HRT.

HRT	Felt Better	Felt Worse
Current users	81 (74%)	5 (5%)
Past users	10 (34%)	13 (45%)

p<.001

Gass M. *Menopause*. 1997:4(1);19.

Bleeding

Women of all ages cite bleeding as an undesirable side-effect, but it appears to be especially bothersome to older women. Among women over 65 years old, 52% discontinued HRT because of bleeding while only 29% of women younger than 56 stopped HRT because of bleeding.[17] In one study, the discontinuation rate increased in women with increasing age

among those who had a uterus, but not among those who did not have a uterus.[18]

Age

Age plays a role in both initiation and continuation of HRT. Data collected from various sources indicate that 35% of women aged 40 to 60, 15% of women over 65, and 7% of women over 80 use HRT.[19] It is not surprising that younger women (age 50 to 60) comprise the largest group using HRT since they are the most symptomatic and thus derive the most tangible benefit. The most commonly cited reason for initiating HRT among younger women is vasomotor symptoms. Among older women the most common reason for initiating HRT is concern about osteoporosis.[17] When the tangible benefits sought by younger women are no longer a factor, older women would be more likely to notice the undesirable side-effects of HRT. When considering age at which HRT is initiated, every five years of older age increases the relative risk of discontinuation by 10%.[4]

A survey of women 50 to 55 years old found that 64% stopped using HRT because of side-effects. In the group of women 10 years older, 87% discontinued treatment because of side-effects.[17] Those side-effects mentioned most often were bleeding, breast tenderness, and bloating. Results from one small study found that only 5% of current users felt worse on HRT while 45% of past users reported that they felt worse on HRT[20] (Figure 3). Collectively, these findings illustrate that how women feel on HRT is very likely to affect the continuation rate

Other Side-Effects

Other factors causing women to discontinue HRT are weight gain and fear of breast cancer. Weight gain is very common as women age, and women on HRT often mistakenly attribute it to the medication. Information to the contrary can avert an unnecessary discontinuation of HRT. In one study, fear of cancer followed bleeding as the two most common reasons for discontinuing HRT.[21] Although bleeding is usually the number one reason for discontinuation, the other factors are variably ranked depending on the study.

In some studies women with higher education and/or higher socio-economic classification were more likely to use HRT.[1,22] Low-income African-American women have been found to have the same rate of symptoms, but the women did not perceive the symptoms to be bothersome.[23] This may explain in part why African-American women are less than 1/3 as likely as other races to continue HRT beyond five years.[1] How well-informed various subpopulations are about their particular lifetime health risks and the potential preventive aspect of HRT may also play a role in their use of HRT.

The highest rate of discontinuation of HRT is during the first six months of use. The discontinuation rate is higher in those women with an intact uterus. Continuation can be improved 10% to 20% by switching to another regimen[18] (Figure 2). Although transdermal therapy is widely used in Europe, in the United States it is associated with a higher rate of discontinuation; however, 25% of women discontinuing transdermal therapy are willing to switch to oral therapy, while only 0.9% of women discontinuing oral HRT will switch to transdermal.[17]

> "Adherence to HRT is similar to adherence to other medications. Discontinuation is high in the first six months."

GENERALIZATIONS

Several generalizations can be drawn from these studies. Adherence to HRT is similar to adherence to other medications. Discontinuation is high in the first six months. Side-effects and fear of cancer contribute to discontinuation. Bleeding is a principal cause of discontinuation. Older women are more likely to discontinue HRT. Being aware of these generalizations allows one to modify clinical practice in order to minimize the discontinuation rate. First and foremost a woman needs to have a clear understanding of why she is initiating or continuing HRT. If she does not perceive the benefits to be worth the side-effects or if she does not perceive the benefits to be greater than the cost and effort of taking a medication, it is unlikely she will become a long-term user.

RECOMMENDATIONS

Information tailored to each woman's health profile and to her particular preferences will be the mainstay of the HRT decision-making. A woman's attitude toward bleeding or breast tenderness may influence the estrogen dose or the way in which the progestogen is incorporated. Women with a uterus may need to be seen more frequently in the first six months.

The issue of breast cancer should be addressed. Since most women know one or more women in their 50s with breast cancer, it is a subject of significant concern for many patients. The meta-analysis of worldwide data on HRT and breast cancer provides a comparison easily understood by patients; namely, that the patient's risk of getting breast cancer with use of HRT is less than her risk of getting breast cancer if her own natural menses were to continue indefinitely.[24]

The older women constitute another group who may need to be seen more frequently. Their increased likelihood to discontinue treatment because of side-effects suggests that lower doses may be advisable initially. Frequent visits early in the course of treatment afford the opportunity to address their concerns, answer questions, provide reassurance, and change the treatment regimen when indicated.

Use of culturally relevant information for subpopulations would be ideal. Accurate data for these groups may require waiting for the results of the large ongoing trials, such as the Women's Health Initiative. In the meanwhile, assisting all patients in clarifying their healthcare priorities and providing them with our most current data regarding HRT and preventive care measures is a starting point.

With the vast array of HRT products on the market, the clinician has many options from which to select the one most suited to the patient's situation. It can be modified based on feedback from the patient. HRT is still an evolving story. Eligible patients should be informed that no decision is final. HRT can be revisited each year as new data become available.

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Risks of Deep Vein Thrombosis in Hormone Users

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INTRODUCTION

Conclusions influencing clinical decisions about the effects of hormone replacement therapy (HRT) on thrombotic risk have undergone major revisions over the last 30 years. Assumptions in the 1970s were that there was not convincing evidence that low dose HRT is associated with increased risk for venous thromboembolism (VTE).[1,2] However, data in the past several years from several observational studies and one clinical trial have suggested that postmenopausal hormone replacement therapy increases risk for venous thromboembolism.[3-6]

ESTROGEN AND VTE RISK

In the observational studies, the risk is two to fourfold increased in women taking estrogens compared with non-users. Each of the observational studies included statistical adjustments for potential confounders such as age, weight, and cigarette smoking. All studies contained only women who did not have known risk fac-

tors for venous thromboembolic events. The incidence among women in these studies was about 1-2/10,000 woman years. Because women at high risk (prior venous thromboembolic events, cancer, recent surgery, immobilization, and chronic medical conditions) were excluded, the true incidence in unselected women is likely higher.

Several studies report incidence of 6-18/10,000. A recent study using phlebography found an incidence of 16/10,000 per year. In women 50 years and older the rate was 34/10,000, and in those 60 years and older the rate was 42/10,000.[7]

The Heart and Estrogen/progestin Replacement Study (HERS) has recently suggested that HRT increases the risk in patients with known coronary heart disease (relative hazard, 2.7 [95% CI, 1.4 to 5.0] [P = 0.003]; excess risk, 3.9 per 1000 woman years [CI, 1.4 to 6.4 per 1000 woman years]; number needed to treat for harm, 256 [CI, 157 to 692]). In multivariate analysis, the risk for venous thromboembolism was increased among women who had lower extremity fractures (relative hazard, 18.1 [CI, 5.4 to 60.4]) or cancer (relative hazard, 3.9 [CI, 1.6 to 9.4]) and for 90 days after inpatient surgery (relative hazard, 4.9 [CI, 2.4 to 9.8]) or non-surgical hospitalization (relative hazard, 5.7 [CI, 3.0 to 10.8]). Risk was decreased with aspirin (relative hazard, 0.5 [CI, 0.2 to 0.8]) or statin use (relative hazard, 0.5 [CI, 0.2 to 0.9]).[8,16]

PROGESTINS AND VTE RISK

There is relatively little information on the effects of progestins given alone in relation to VTE. Data are based on small incidence rates. Overall, there appears to be a modest, non-significant, positive association between exposure to progestins alone and venous thromboembolism.[10,11]

Vasilakis et al studied a cohort of 74,086 women from a general practice research database who were treated with an oral or an injectable progestin by a nested case-control analysis. The relative risk estimates were 1.3 (0.3-6.8) for progestogens used alone as a contraceptive and 5.3 (1.5-18.7) for progestogens used alone for other reasons. Overall, there was a modest non-significant positive association between exposure to progestogens alone and VTE.[9] The absence of an effect when the progestogens are used alone for contraception compared with when they are used for gynecologic disorders suggested to them that the gynecologic disorders and the higher doses of progestogens may be associated with increased risk of VTE.

SERMS AND THE RISK OFVTE

The use of selective estrogen receptor modulators (SERMS) does not avoid the risk of thromboembolism. Tamoxifen in clinical trials is associated with increased rates of stroke, venous thromboembolism, and pulmonary embolus.[12] In the very large MORE study[13] which examined the effects of raloxifene on bone density and fracture rates in postmenopausal women, raloxifene increased the risk of venous thromboembolic disease [relative hazard 3.1(.5-6.2)]. Raloxifene, tamoxifen, and estrogen increase the risk of VTE to a similar degree. The risk is variable depending on the clustered risk factors, and it goes up with age. For example, the risk is higher in women given any of these preparations when they already have confirmed coronary artery disease.

The increased risk probably involves alterations in the hepatic production or metabolism of coagulation factors, although the exact mechanism remains to be elucidated. For some women, this risk may be relatively high as outlined above. Less potent risk factors for VTE are obesity, hypertension, and in some studies, smoking.[14] Certain inherited conditions, including deficiencies of antithrombin III, protein C and protein S, elevated serum antiphospholipid antibodies, and the factor V Leiden abnormality are also associated with increased risk for venous thromboembolism. Because each disorder is uncommon, at present it appears reasonable to confine laboratory screening to the minority of women (under 1%) who have a history or a family history of VTE.[15]

CONCLUSION

The recent reports noting that some menopausal patients may have an increased risk for VTE following HRT administration have made decisions by doctors and their patients regarding the long-term use of HRT more difficult. We need the stability that only further randomized controlled trials (RCTs) can now provide. As we await the outcome of the Women's Health Initiative, women in these clinical trials are being advised to discontinue HRT pre-operatively and during immobilization due to fracture, stroke, or other severe illness. Women with a history of venous thrombosis or pulmonary embolism should not take raloxifene, tamoxifen, or estrogen. Women currently taking any of these medications should discontinue them four to six weeks before major surgery or during periods of immobilization. Women using these medications should be instructed on ways to prevent problems with VTE in general, for example ambulating to avoid sitting too long while traveling in an airplane, etc.

The risk of VTE with HRT is quite acceptable in women who have no risk factors regardless of their age. Nevertheless, this risk should not be distorted or minimized when discussing the overall risk/benefit of menopausal hormone choice.

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Effects of Hormone Replacement Therapy on Clinical Fractures and Height Loss: The Heart and Estrogen/ Progestin Replacement Study (HERS): A Review

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The Heart and Estrogen/progestin Replacement Study (HERS) is a randomized, placebo-controlled clinical trial designed to evaluate the effect of hormone replacement therapy (HRT) on recurrent cardiovascular events in women with significant pre-existing heart disease. In the April issue of the *American Journal of Medicine*, the HERS investigators[1] report their analyses of the secondary endpoint of fracture. This study evaluated radiographically documented clinical vertebral and non-vertebral fractures, height, and, in a subset of participants, bone mineral density (BMD). The authors reported there was no evidence of a reduction in the incidence of fractures or rate of height loss in these older women not selected for osteoporosis. The relevance of these findings can be questioned in several ways.

First, the population enrolled consisted of 2,763 women with cardiovascular disease, the majority of whom did not have osteoporosis (about 85%); the mean T-score in the sub-population measured being –1.4 in both placebo and HRT groups. Recent studies of bisphosphonates have demonstrated how difficult it is to confirm fracture efficacy in women who do not have osteoporosis.[2,3] Indeed, Cauley et al note in their discussion that similar findings had been reported for alendronate.[3] Furthermore, the study design was limited in its ability to detect vertebral fractures, which are the most common fractures associated with osteoporosis. Analysis of the HERS data was limited to painful, clinically recognized, and radiographically confirmed vertebral fractures, which represent, as cited by the authors, about one-third of the total number of vertebral fractures. Thus, the statement by the HERS authors that "the rate of clinically evident vertebral fractures was also much lower than in those reported in trials carried out in osteoporotic populations" does not come as a surprise to those of us who conduct clinical trials investigating osteoporosis.

In their discussion of the influence of HRT on height loss, the authors indicate their data "are consistent with the hypothesis that estrogen/progestin may prevent height loss in a group of osteoporotic women." Their alternative hypothesis that there was not sufficient power to see an effect of height loss due to the low fracture incidence in this population of older menopausal women is also raised in their conclusion regarding fracture risk. This also is consistent with bisphosphonate studies in which prevention of height loss is most obvious among those who develop morphometric vertebral fractures.[4]

HERS is a randomized clinical trial for the evaluation of HRT on recurrent cardiac events in older women with documented cardiovascular disease, with limited power to detect moderate reductions in fracture risk. Additionally, it did not measure proper endpoints to assess this risk. The attempt to generalize from HERS about the potential effect of HRT on fracture risk in aging female populations at risk of osteoporosis-related fractures does not seem to be reflective of sound evidence-based medicine.

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