



Menopause and Hormone Therapy

What We Recommend To Our Patients and Why

First, *menopause* is a natural transition that all women will experience around the end of their fifth decade of life. It occurs when the ovaries stop functioning and estrogen and menstrual cycles cease. *Perimenopause* is the interval of time prior to menopause in which women may experience changes in their menstrual pattern, periodic emotional feelings or hot flashes. These symptoms are due to declining ovarian function, which may be intermittent or continuous. The life expectancy of women born prior to the 1920's was less than 50 yrs. Today, a healthy woman at the age of 50 has the opportunity to live over 30 more years of life. The quality of those years is our priority, so they may be lived to the fullest.

Second, heart attack and stroke (due to atherosclerosis or 'hardening of the arteries') has become the number one cause of death in women. Statistics show that 1 in 29 deaths among women are due to breast cancer compared to 1 in 2 deaths due to cardiovascular disease. Yet, the media has principally focused on cancer (breast, ovary, colon) and osteoporosis as the most important health issues in women. Of all the factors that contribute to the risk of a woman developing any of these diseases, estrogen has received the greatest medical and media attention. In the past decade there have been many national and international studies published on the role of hormone replacement treatment (estrogen and progesterone) in menopausal and post-menopausal women with seemingly conflicting outcomes. Many books written by 'authorities', including physicians, frequently reflect their personal biases. It is no wonder that confusion and even fear influences the decisions of both women and general physicians as to the appropriate use of hormone therapy.

On October 15, 2004 the Executive Committee of the International Menopause Society issued its revised Position Statement regarding hormone treatment entitled: **"Guidelines for Hormone Treatment of Women in the Menopausal Transition and Beyond"**. A summary of this report follows, but first, a few key points of information:

- A hormone is a substance (e.g. insulin, thyroid, estrogen, testosterone, cortisone) that is produced by a specific organ and transported in the bloodstream to tissues that have specific hormone receptor sites (similar to the space shuttle docking with the space station). Tissues vary in how dependent they are on having their receptor site "docked" by their hormone in order to function normally. For example, inadequate insulin production results in diabetes mellitus. Similarly, in the absence of thyroid or cortisone hormones, the body's metabolism would cease to function and death would result.
- Estrogen and progesterone are natural hormones produced by the ovaries during the reproductive years. They are responsible for normal female physical and sexual development and function, including reproduction.
- Body tissues that also have estrogen receptors include the vagina, vulva, bone, muscles, skin, arteries, brain, and intestines.
- The result of the absence of estrogen on these tissues varies between the tissues and between women. The vagina, vulva and bone are very estrogen dependent, while the skin, intestines, brain and arteries varies with other influences, including genetic.
- Estrogen is not a youth preserving hormone, but it is necessary to preserve the maximal possible health and function of these tissues.
- Only hormone therapy will completely eliminate the symptoms of menopause, including hot flashes, night sweats, and any associated emotional and mental symptoms. Herbal supplements will not.

- The term “Bio-Identical” refers to a hormone that is *identical* to the hormone produced by the body.
- **ERT** means ‘estrogen replacement therapy’ and refers to taking estrogen either cyclically (usually the first 25 days of each calendar month) or continuously (daily without stopping).
- **HRT** means ‘hormone replacement therapy’ and refers to taking estrogen plus a progestin (synthetic) or progesterone (bio-identical). HRT is indicated when a woman has her uterus. HRT is taken either cyclically or continuously.
- **MHT** means ‘menopausal hormone therapy’ and includes both ERT & HRT.

When estrogen deficiency occurs and is no longer available to stimulate the receptor sites on all the body tissues discussed previously, there are two general groups of changes that begin to occur. For simplicity these changes can be categorized as **symptomatic** and **asymptomatic**. There are three main categories in the symptomatic group, and includes those feelings that may occur suddenly and be of short or long duration. The asymptomatic group is insidious, as these physical changes occur slowly and usually occur without any symptoms until they are at an advanced stage.

A. Symptomatic Group

1. Vasomotor Symptoms:

- a. Hot flashes
- b. Perspiration and night sweats
- c. Palpitations

2. Physical Changes:

- a. Vagina: dryness, itching and irritation; painful intercourse
- b. Bladder: over-active bladder symptoms or frequent urinary tract infections
- c. Skin: dryness, wrinkles, thinness, decreased collagen
- d. Arthralgia (Joints): aches or pain in the body’s joints
- e. Myalgia (Muscles): aches or pain in the muscles
- f. Decreased breast size

3. Changes in Brain Metabolism:

- a. Irritability
- b. Lethargy: lack of mental or physical energy
- c. Mood swings
- d. Difficulty concentrating
- e. Short-term memory loss
- f. Insomnia or poor quality sleep
- g. Depression
- h. Decreased libido (decreased sexual desire)

B. Asymptomatic Group

Physical changes that can occur in the absence of circulating estrogen:

1. Osteoporosis (Bone): thinning of the bones
2. Memory loss and Alzheimer’s Disease (Brain)
3. Risk of colorectal cancer (Colon)
4. Macular degeneration (Eye): resulting in blindness
5. Cardiovascular Disease caused by atherosclerosis (hardening of the arteries)

The International Menopause Society issued their Revised Statement on October 15, 2004, after a thorough analysis of all the published studies about hormone replacement therapy and its benefits and risks. The following is their report of their findings and recommendations. They are consistent with the recommendations of the professional medical staff at the Gunn Center of Gynecology.

“Guidelines for Hormone Treatment of Women in the Menopausal Transition and Beyond”
Position Statement by the Executive Committee of the International Menopause Society
Revised October 15, 2004

“Recent communications regarding estrogen or estrogen+progestin treatment and clinical cardioprotection (heart), breast cancer risk and cerebral aging have produced considerable confusion and concerns among women, care-givers and the media. The actions of the FDA and other National Safety of Medicine Boards in response to the publication of data from the Women’s Health Initiative (WHI) and the Million Women Study (MWS) have also raised concerns. The Executive Committee of the International Menopause Society (IMS) has reviewed all presently available information from observational studies, randomized controlled trials (RCTs) and preclinical research, and wishes to point out the following:

1. WHI Studies - the small differences in absolute numbers of events between groups during the trial makes conclusions regarding the possible value of HT (estrogen + progesterone) highly uncertain and devalues or invalidates the conclusions from the initial publication from which so many clinical implications have been drawn (by the media and general physicians).
2. In contradistinction to the estrogen+progestin arm (of the WHI Study), the women taking only estrogen had a 23% lower incidence of new invasive breast cancers than did the placebo group.
3. Therefore, at present, the only valid studies of *menopausal hormone therapy* (MHT) for cardioprotection of women in the menopausal transition are the epidemiological and observational studies that generally agree with laboratory and animal studies, indicating cardioprotection by estrogen when initiated (early) in women during the menopausal transition.
4. In summary: The HT (hormone therapy) RCTs (studies) reported to date cannot indicate that estrogen or estrogen+progestin treatment started during the normal menopausal transition is effective for primary prevention of cardiovascular disease or other long-term consequences of sex steroid withdrawal.”

“With the above in mind, the Committee proposes the following guidelines for addressing these issues for women during their climacteric (menopause):

1. The Executive Committee recommends the continuation of presently accepted global practice, including the use of estrogen+progestin or estrogen alone in the case of women who have undergone hysterectomy, for the relief of menopausal and urogenital symptoms, avoidance of bone wasting and fractures, and atrophy of connective tissue and epithelia (skin and vagina). Possible clinical benefits in the prevention of cardiovascular disease and nervous system protection seem likely, but have yet to be confirmed.
2. There are no new reasons to place mandatory limitations on the length of treatment, including arbitrary cessation of HRT in women who started replacement during the menopausal transition and remain symptom-free while on hormones. Judging from the accelerated rate of cardiovascular events after premature menopause and the loss of cardioprotection after stopping MHT, such cessation may even be harmful.
3. Each patient must be counseled about the current data on the risks and perceived benefits of HRT so that she can make appropriate, informed, individual decisions about continuing or stopping treatment.
4. The risk of complications of MHT remains an important clinical issue; there are no general guidelines that apply, except to indicate that MHT, both estrogen+progestin and estrogen-alone, has been associated with a small absolute increase in deep venous thrombosis with subsequent stroke and pulmonary embolism. The WHI continues the trend of conflicting effects on breast cancer (a small absolute increase in the estrogen+progestin arm and a decreased risk in the estrogen-only arm) and yet confirms the reduction in the risk of colorectal cancer and bone fractures, including hip fractures. However, cancer, metabolic diseases, vascular disease and brain dystrophy are not only the concerns of women on MHT, but are of universal concern to (all) women past the age of reproduction.

5. The use of hormones/hormone substitutes as part of the care of the aging population will be a subject of increasing importance in both sexes. (The following) governing principles for enhancing the length and quality of life (for women) are emerging:
- (a) Prevention, not treatment, is the most feasible goal. Use of hormone/substitutes should be part of an overall strategy including life-style modification and other preventive measures, especially cessation of smoking and alcohol abuse.
 - (b) There is no evidence that HT is beneficial for existing heart disease or dementia, but the initiation of HRT during the menopausal transition appears to provide protection against complications of the climacteric, such as fractures and potentially heart disease and brain disease. This conclusion is based on observational studies and pre-clinical trial research, since no RCT's (randomized clinical trials) have adequately addressed women starting treatment during the menopausal transition. Specifically, a WHI derivative study on dementia is not considered of value in this decision, because of the late start of HT, the lack of changes in minimal cognitive dysfunction and the possibility that subjects in this thromboembolism-prone group developed vascular dementia rather than Alzheimer's disease.
 - (c) The dose and regimen of HRT needs to be individualized. Older menopausal and postmenopausal women generally require lower doses than younger women.
 - (d) The effect of the route of administration remains an issue. Avoidance of the first pass effects of oral therapy may be advantageous, especially for those with increased risk factors for venous thrombosis.
 - (e) Progesterone/progestins are only required for protection of the endometrium (of the uterus)."

"We are facing a tide ('baby-boomers') of post-reproductive women entering menopause. In addition to prevention by changes in life-style and dietary management, HRT remains a principal tool in preventing illness and maintaining quality of life in this population; therefore, it must be the subject of continuing scientific investigation."

In Light of This Current Analysis, Who Should Consider MHT?

Women of all ages should be evaluated as to their risks of heart disease, stroke, osteoporosis and cancer. Balancing the beneficial and potential harmful effects of any treatment is an important task for making informed decisions. We believe that given the current understanding of the positive role of MHT in improving quality-adjusted life expectancy, women should give strong consideration to initiating MHT when either menopausal symptoms develop or menstruation stops.

Treating Menopausal Symptoms

Estrogen is the only effective therapy in the treatment of the following symptoms and physical changes:

- Reversible vasomotor symptoms, including hot flashes, night sweats and palpitations
- Vaginal atrophy (thinning of the vaginal wall), which often results in painful intercourse, over-active bladder symptoms and frequent urinary tract infections
- Symptoms due to changes in brain metabolism

If any of these symptoms are interfering with the quality of a woman's life, MHT should be strongly considered. The body does not store estrogen, so replacement may be required for several years. Estrogen can be given orally (pill), applied to the skin (patch or gel), by injection or inserted vaginally by tablet (VagiFem), ring (Femring) or cream. The non-oral route may be preferable in women with abnormal triglyceride levels, liver disease, gallstones, migraine headaches or an increased risk of blood clots. MHT does not cause weight gain in postmenopausal women. If a woman decides not to use MHT and has symptoms associated with vaginal thinning (atrophy), estrogen used vaginally will restore the lining to a normal condition. Studies have demonstrated that no significant absorption into the blood stream occurs when low dose estrogen is administered vaginally. Non-hormonal medications that can be effective include the anti-depressant group of drugs call SSRIs and Gabapentin (Neurotin).

A note about *Phytoestrogens*, naturally occurring plant or food substrates (e.g. wild yam extract and black cohosh) sold OTC (over-the-counter) and are functionally similar to a weak form of estrogen. They generally have the same effect as a placebo and are not an adequate alternative to estrogen in relieving menopausal symptoms. Women frequently believe that these products are safe, because they are plant derived. While these products are all found in natural environments, they are not *bio-identical*. Further, they are unregulated regarding their safety, quality or potency control. It is important to recognize that estrogen hormone products used in MHT are derived from plant or animal sources.

Role of Estrogen in Reducing the Risks of Coronary Heart Disease and Stroke

The cause of coronary heart disease and stroke is atherosclerosis, which results from a build-up of cholesterol deposits in the arteries called *plaque*. Atherosclerotic plaque can become unstable, rupture and cause a blood clot to form, thereby reducing the amount of blood flow to the heart muscle (causing chest pain or a heart attack) or to the brain (causing a stroke). For a thorough review of this important subject, request a copy of our article entitled: '*Cholesterol and Your Risk of Heart Disease and Stroke*' or visit our web site: www.gunncenter.com.

As mentioned earlier, atherosclerotic heart disease is the No. 1 killer of women. According to the American Heart Association ("AHA"), heart attack and stroke has killed more women than men in every year since 1984. The mainstay of reducing the risk of coronary artery heart disease and stroke is the modification of personal lifestyles and the diagnoses and treatment of high blood pressure, diabetes and elevated cholesterol. A regular and proper diet (as recommended by the AHA), a program of aerobic exercise, not smoking, keeping body weight in a normal range and taking nutritional supplements are the keys to a healthier life and longevity.

Estrogen has long been viewed as playing an important role in reducing the risks for heart attack by maintaining a healthy artery lining, raising the 'good' HDL-cholesterol and lowering the 'bad' LDL-cholesterol. Recent studies found that women who started MHT after having a heart attack (referred to as *secondary* cardio-prevention) did not experience any benefit against future heart attacks after 5 years of use. However, the IMS Position Statement (reviewed above) states: "epidemiological and observational studies generally agree with laboratory and animal studies, indicating the benefit of *primary* cardioprotection by estrogen, when initiated (early) in women during the menopausal transition."

Preventing Osteoporosis

Osteoporosis is a disease in which the bones become thin and porous and are subject to a high risk of fracture, especially the spine, hip and forearm. *Osteopenia* is a less severe form of osteoporosis. According to the National Osteoporosis Foundation, osteoporosis is reaching epidemic proportions in the United States. Bone mineral density ('BMD') decreases rapidly in women within 5 years of entering menopause. This is due directly to estrogen deficiency. The American College of Obstetrics and Gynecology has indicated that estrogen is the first-line therapy for the prevention of osteoporosis. A non-estrogen drug called *Evista* (Raloxifene) is an alternative to taking estrogen and helps prevent and treat bone loss (osteopenia and osteoporosis). Bone loss can additionally be treated with biphosphonates (Fosamax or Actonel).

What About the Possible Risks of HRT?

Cancer of the Breast

The majority of women believe that breast cancer is the leading cause of death in the United States for women aged 65 years and older. In truth it is responsible for less than 4% of deaths in women. The risk of breast cancer increases primarily with age and with a positive family history. A statistic often quoted is: 1 of every 9 women will develop breast cancer. While this is true, it applies only to women who are in their 90's. Importantly, early detection of breast cancer has resulted in a cure rate of over 95% in women with localized disease.

The largest overall assessment for breast cancer risk among non-estrogen and estrogen users is a collaborative review of 51 studies from 21 countries published in 1997. There were 52,705 women with and 108,411 women without breast cancer. The use of estrogen for 5 years was associated with an estimated

increase risk of 2 cases of breast cancer for every 1000 women after 5 years and 6 cases for every 1000 women who used estrogen for over 10 years. Interestingly, the biology of a breast cancer is different in those women who used estrogen. Their tumors were more likely to be found earlier, less likely to have spread to the lymph nodes and therefore, had a better prognosis. More recently, the WHI study of estrogen alone (without progesterone) showed a *reduced* incidence of breast cancer (refer to page 3, #2). The use of estrogen in women who have had breast cancer is reviewed in a separate article entitled: '*Estrogen Therapy in Breast Cancer Survivors*'. Request a copy or visit our web site: www.gunncenter.com.

Cancer of the Uterus (Endometrium):

Studies have shown that women who have their uterus and take estrogen alone have an increased risk of developing endometrial cancer. If progesterone is given in addition to the estrogen, this increased risk is eliminated. Since their physicians closely monitor patients who are on ERT or HRT, any potential endometrial abnormality is usually found before it becomes an actual cancer. If a woman has had a hysterectomy, there obviously is no risk. Studies have demonstrated that the use of birth control pills during the reproductive period of a woman's life decreases the future risk of endometrial cancer by about 50% for up to 15 yrs. after stopping the pill.

Cancer of the Ovary:

Cancer of the ovary is called the silent killer, because it produces no symptoms until it has reached an advanced stage. Every year, about 23,000 U.S. women are diagnosed with ovarian cancer and 14,000 women die from this disease. A woman's lifetime risk of developing ovarian cancer is 1.7 percent. This means that in a group of 100 women followed from birth to age 90, fewer than two would get ovarian cancer. In comparison, 13 women would get breast cancer, and close to 32 would develop osteoporosis. A recent study suggests that women on moderately high doses of estrogen alone for over 10 to 20 years had a very small increase in risk for ovarian cancer. No other study has demonstrated any increased risk. It is clear that the use of BCP during the reproductive years decreases the risk of ovarian cancer by 40-80%, and this decreased risk persists for at least 15 yrs after discontinuance of the pill.

Currently, there are no specific screening tests for ovarian cancer. Most ovarian cancers are currently detected on a pelvic examination and are usually at an advanced stage. A blood test called a CA-125 is used as a tumor "marker" in a woman who has been previously treated for ovarian cancer. It is not a *routine* screening test. Neither is it specific for cancer of the ovary as the CA-125 may be elevated from other diseases, and it frequently is normal in the presence of early cancer of the ovary. Early detection of ovarian cancer is most frequently found by pelvic ultrasound, well before it causes symptoms or is detected on pelvic examination. Many women are choosing to have a screening pelvic ultrasound each year just as they have an annual screening mammogram for breast cancer.

Blood Clots

Blood clots in the veins are called *venous thrombosis*. When a blood clot breaks loose and travels to the lungs, the condition is called venous thrombo-embolism ("VTE") and can be fatal. Studies indicate there is a very slight (2-fold) increase in the risk in women on MHT (refer to page 4, #4) and this is age related. Aspirin or statin drugs may lower this risk. Caution should be exercised when using MHT in women who are at high risk for VTE, including a history of prior VTE, lower extremity fractures, or a current cancer. MHT should be discontinued prior to any anticipated period of physical inactivity; e.g. prolonged hospitalization.

Stroke

Studies indicate that postmenopausal women taking MHT have a small but real increased risk of stroke. Whether the type of hormone preparation, dosage, or route of administration modifies this increased risk has not been established by randomized controlled clinical trials.

Our Recommendations:

Women of all ages should be evaluated as to their risks of heart disease, stroke, osteoporosis and cancer. Balancing the beneficial and potential harmful effects of any treatment is important for making informed health

decisions. We believe that given the current understanding of the positive role of hormone replacement in improving quality-adjusted life expectancy, women should give strong consideration to initiating hormone therapy when they enter the menopausal period of their lives.