

Menopause & Hormone Therapy – Updated 2017

In 2012 there were two important medical articles that brought clarity to over a decade of fear and confusion regarding the risks and benefits of hormone therapy in postmenopausal women. These long-term follow-up studies (included patients originally enrolled in the WHI Study) have now established that the use of estrogen (when initiated within 5 years of menopause) is not only safe, *it is statistically protective against breast cancer, heart disease and all causes of death!!!*

- **Heart Disease:** A prospective study of women receiving **hormone replacement therapy** (HRT) early after menopause had a significantly (50%) reduced risk of mortality, heart failure, or myocardial infarction and without any apparent increase in risk of cancer, venous thromboembolism (blood clots), or stroke. (Ref. #26).
- **Breast Cancer:** A long-term follow-up of the WHI study (Women's Health Initiative) found that estrogen alone reduced both breast cancer incidence and breast cancer mortality in women while on therapy and for 5 years after discontinuing therapy. (Ref. #25)
- **All-Cause Mortality:** Reduced by 60%. (Median follow-up of 11.8 years, Ref. #25)

In **April 2011** the Journal of the American Medical Association (JAMA) published a follow-up study of the women in the WHI study who took estrogen alone and the incidence of breast cancer. (Ref. #2) The finding: a statistically significant reduction of 23%. Further, those women who did develop breast cancer were 63% less likely to die from their disease. There was NO increased risk for heart attack, stroke, blood clots, hip fracture and colon cancer.

The **2012 review** of the WHI study (Ref. #25) confirmed these finding and reported a 60% reduction in the mortality from *all-causes* of death. The North American Menopause Society has released a statement that supports these findings, stating, “combination hormone therapy (both estrogen and progesterone) initiated around the time of menopause is safe”.

In **May 2013** the British Menopause Society published their updated review and concluded (1) HRT should be individualized, (2) arbitrary limits should not be placed on the duration of usage, (3) HRT prescribed before the age of 60 years of age has a favorable benefit/risk profile, and (4) “It is imperative that women with premature menopause are encouraged to use HRT. (Ref. #27) This was reinforced and published in 2014 in the ACOG Practice Bulletin No.141 (Ref. #35)

These recent studies contradict the continuing *mistaken belief* of both patients and health care providers that estrogen is dangerous because it causes breast cancer and increases the risk of heart disease. As long as uncertainty about the safety (not the benefits) exists, many physicians continue to err on the side of refusing or discouraging women to initiate or remain on estrogen therapy in spite of the current knowledge.

A Little Background

Menopause is a natural occurring event that all women will experience (usually in their early 50's) when their ovaries cease functioning. This results in a loss in the ability to bear children and the loss of estrogen production. *Post-menopause* is diagnosed when a woman has not menstruated for one year. *Peri-menopause* is diagnosed when the menstrual cycles still occur, but vary in frequency and length and may be associated with psychological, emotional and/or physical symptoms (discussed later). These symptoms or disturbances are directly due to declining ovarian production of estrogen, progesterone and testosterone. This variability in estrogen levels may be periodic or continuous. This is why many women who are “still menstruating” can be estrogen deficient and experience symptoms.

Women born up to the 1930's had a life expectancy of about 50 yrs. Today, a woman can expect to live well into her 80's with over one-third of her life continuing after menopause and be subject to the physical changes discussed later in this paper.

Women's Health Initiative (WHI) Study

The history of hormone replacement in women has seen many swings in popularity over the past several decades. In 1991 the National Institutes of Health (NIH) launched the Women's Health Initiative (WHI) Study involving *161,808 healthy postmenopausal women* aged 50-79 years with an average age of 63 years. The study was designed to test the effects of hormone therapy on heart disease, bone fractures, breast cancer and colon cancer. Three groups were followed:

- (1) **Estrogen** replacement group of women who had *undergone a prior hysterectomy* received a naturally occurring estrogen (Premarin) taken orally without progesterone and is referred to as the **ERT** group.
- (2) **Estrogen+Progesterone** replacement group of women received a combination of Premarin and a synthetic progestin (Provera) in the form of PremPro. This form of replacement is referred to as **HRT**.
- (3) **Placebo** group, which contained no hormone.

In 2002 the WHI study was stopped prematurely because the Estrogen + Progesterone group of women was found to have a slightly higher incidence of breast cancer, heart attack, stroke and blood clots. The data for the Estrogen group did not show these adverse events. However, the medical profession and lay press did NOT differentiate between the ERT and HRT groups. Rather they were simply grouped together and referred to as "estrogen". Millions of women in the U.S. stopped filling their ERT and HRT prescriptions, decreasing from 61 million prescriptions written in 2001 to 21 million in 2004. Fear of possible breast cancer, heart attacks, and blood clots resulted in "hot-flash hell" for millions of women.

Importance of Estrogen

When a woman is considering hormone replacement therapy (ERT or HRT), it is critical that she clearly understand the important role that estrogen and progesterone have played throughout her normal reproductive life. Young girls' *secondary sex characteristics* develop in the early part of her second decade of life and is followed within two years by the onset of menstruation (menarche). This primary estrogen produced by the ovary during a woman's reproductive years is *estradiol*. Estrogen receptor sites are present on the surface of cells of most of the tissues in a woman's body. Estrogen's attachment to these receptor sites is important for optimal cell function. In the absence of estradiol these cells begin to undergo varying degrees of accelerated aging that may not clinically appear until years later. Specific estrogen receptors are found in the endometrium (the lining of the uterus), ovaries and vagina as well as the brain, bones, arteries, intestines, kidneys and skin. Certain tissues are completely dependent on estrogen for normal growth and optimal function, (i.e. vagina and endometrial lining of the uterus). In the absence of circulating estrogen a woman's organs and body tissues undergo significant changes resulting in acceleration in the aging of those tissues and organs. It is well established those 5 years after menopause the incidence of bone loss (osteoporosis) and heart attacks rises significantly (equally that of men).

As a woman's ovarian function begins to fail during peri-menopause, the circulating estrogen levels decline and a woman usually experiences symptoms of varying severity. The more common estrogen dependent symptoms are listed below as *symptomatic*, and includes feelings or sensations that may occur gradually or suddenly and may be intermittent or continuous. The slow changes that occur in the organs and tissues are referred to as *asymptomatic*. These asymptomatic changes are actual physical changes that occur slowly and usually without any symptoms until they are at a more advanced and irreversible stage. It is important to understand that estrogen is necessary for the normal function of a woman's body, including the monthly stimulation of the endometrium of the uterus during the reproductive years. Progesterone is produced by the ovary after ovulation and prepares the endometrium to support a possible pregnancy. When pregnancy does not occur, the endometrial lining sheds in the form of a menstrual period. Progesterone's use in hormone replacement is for the protection of the endometrial lining of the uterus to prevent its' excessive growth and possible cancer. As noted in the WHI Study, progesterone is not indicated for those women who have had a prior hysterectomy.

A. Symptoms:

1. Vasomotor:

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

2. Physical:

- a. Heart palpitations
- b. Itching, dryness and irritation of the vagina
- c. Decreased libido (decreased sexual desire)

- d. Painful intercourse
- e. Over-active bladder symptoms
- f. Frequent urinary tract infections
- g. Skin changes
- h. Arthralgia – aches or pain in the body’s joints (Joints)
- i. Myalgia – aches or pain in the muscles (Muscles)
- j. Decreased breast size
- k. Dry eyes

3. Brain:

- a. Irritability
- b. Lethargy – lack of mental or physical energy
- c. Anxiety
- d. Mood swings
- e. Difficulty concentrating
- f. Short-term memory loss
- g. Insomnia
- h. Depression
- i. Decreased libido (*refer to paragraph below**)

B. Asymptomatic (No Symptoms):

- 1. Osteoporosis – thinning of the bones (Bone)
- 2. Memory Loss, Dementia and Alzheimer’s Disease (Brain)
- 3. Colorectal cancer (Colon)
- 4. Macular Degeneration - resulting in blindness (Eye)
- 5. Cardio-Vascular Disease & Stroke – caused by plaque buildup and rupture (Arteries)

*The issue of a decrease in *libido* or sex-drive during the peri-menopause or menopause is common and may be associated with declining levels of testosterone, which is also produced by the ovary. A decrease in libido is often a reflection of less frequent intimacy in a marriage or relationship. It is often associated with a women’s feeling that she has “insufficient time for herself” and of being “too tired” to even think about sex. A conversation regarding re-establishing “sex” as a priority and setting aside time for intimacy is very important for an emotionally healthy relationship. Intimacy does not always require the act of intercourse for a woman to feel fulfilled. A blood measurement of the testosterone level may suggest if a trial of replacement therapy may improve libido.

Why Do Some Women Escape Symptoms of Menopause?

There is evidence that a “brain-estrogen threshold” may govern the presence or absence of symptoms. Women with a lower brain-estrogen threshold may not experience any symptoms, while a high brain-estrogen threshold (requiring higher blood estrogen levels to access the brain) is associated with early and severe symptoms. Further, symptoms may be increased by too much as well as too little estrogen, fluctuations in circulating estrogen levels or from side effects of progesterone. This is why hormone replacement therapy must be individualized for each patient.

Should Estrogen be Recommended to Control Symptoms and Prevent Future Risks?

Based on the current long-term studies I discussed above, the answer is **YES**. However, this question can only be answered after a thorough evaluation of a woman’s specific symptoms and a discussion and understanding of the risk and prevention of future diseases. When determining a specific program of either ERT or HRT for a patient, a number of factors should be taken into account, including:

- Are menopausal symptoms present?
- Is there a prior hysterectomy?
- Are menstrual periods still occurring?
- Are there any cardiovascular risks for a heart attack or stroke (click here for [Longevity Program](#))?
- Are there risks for osteoporosis (determined by measuring her bone density & family history)?
- Are there any contra-indications to using estrogen replacement (see list below)?

Once a specific menopausal evaluation is performed, including a detailed symptom list and a future disease risk assessment, a trial ERT or HRT can be recommended. The dosage and route of administration is individualized. What the WHI follow-up studies have clearly established is that for ERT or HRT to be most successful, it must be

started within the first few years following the onset of menopause. The benefits of initiating hormone therapy several years (greater than 10) after menopause has occurred are not as great as when started in the perimenopausal years. However, hormone therapy will reverse symptoms at any post-menopausal age.

The question as to how long hormone therapy can or should be used is often raised. There is a growing view among medical organizations that hormone therapy should be individualized and NOT discontinued solely based on a woman's age. The North American Menopause Society (NAMS) released the following statement June 8, 2015: "Medicare Plans, insurance companies and healthcare providers have failed to follow the latest research. Menopausal symptoms are undertreated in women older than 65 years and insurers and clinicians need to shrug off notions of "hard ad fast" rules discouraging hormone use in older women." I strongly believe physicians need to start listening to their patients and stop refusing to provide them educated choices, including hormonal therapy.

What are the Contraindications to ERT or HRT?

- Absolute contraindications include any recent cardiovascular event, suspected pregnancy, or undiagnosed abnormal vaginal bleeding. The presence of thrombophlebitis, severe liver disease, active gall bladder disease, a history of deep vein blood clots or pulmonary emboli (while taking **oral** contraceptives) would require a non-oral route of administration.
- Relative contraindications include a personal history of breast cancer or endometrial cancer.

These contraindications are controversial and initiating ERT or HRT may be appropriate in selected patients. If a woman on ERT or HRT develops any of these events, it is safe to temporarily discontinue her therapy, while considering the severity of any recurring menopausal symptoms.

Treating Menopausal Symptoms

Estrogen is the only effective therapy for eliminating significant vasomotor symptoms (hot flashes, night sweats, palpitations), vaginal atrophy (thinning of the vaginal wall), painful intercourse, over-active bladder symptoms and frequent urinary tract infections. Estrogen may also improve many of the symptoms due to changes in the brain metabolism, including those listed on page 2, A. 3. If any of these symptoms are interfering with the quality of a woman's life, a trial of ERT should be strongly considered. Unless a woman has had a hysterectomy estrogen should not be taken without progesterone to protect against uterine cancer.

The WHI study used an oral estrogen (Premarin), which has now been proven to be safe and protective. The progesterone (Provera) the study used was synthetic (not bio-identical) and was associated with a small increase in breast cancer risk. Bio-identical estrogen and bio-identical progesterone have a molecular structure that is identical to those produced by the ovary and has the same action at the receptor sites of the body's tissues. It is important to note that in this day of generic pharmaceutical drugs (obtained at local or web pharmacies) the purity and actual amount of a hormone may not always be what the label states, even though it is 'FDA approved'. There is a lack of regulation of FDA-approved bio identical hormones prepared by compounding pharmacists. Currently, there are about 8000 pharmacies in the U.S. that compound medications. All 50 states have a Board of Pharmacy that licenses pharmacies within its State. While any pharmacy may compound non-sterile preparations of drugs the standards vary greatly and are generally unregulated. If a patient is going to use a compounding pharmacy for her medication, then I would recommend selecting a pharmacy accredited by the Pharmacy Compounding Accreditation Board (PCAB). The PCAB currently accredits about 200 pharmacies in the U.S. for quality assurance standards that ensure that medications (tablets, capsules, gels and creams) contain exactly what the label states. Web link: www.pcab.org/consumers.

The minimal increased risk of blood clots associated with oral administered hormones is not present with *non-oral* administration, such as applications on the skin (patch, gel or cream), vaginal estrogen rings or tablets, pellet insertion or by injection. Reason: the non-oral route of administration bypasses the liver and therefore, does not trigger any small potential *genetic risk* for blood clots.

Preventing Osteoporosis

Osteoporosis is a disease in which the bones become extremely thin and porous and are subject to 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. An estimated 10 million Americans have osteoporosis and an additional 18 million have osteopenia. Bone mineral density ('BMD') decreases rapidly in women within 5 years of entering menopause and is measured by a simple DEXA screening of

the spine and hips. This loss of bone density is directly due to estrogen deficiency, placing woman at an increased risk for osteoporosis and bone fracture. Numerous clinical research studies have demonstrated the benefits of ERT & HRT with a significant increase in BMD in both the hip and spine and a significant reduction in the incidence of fracture. The American College of Obstetrics and Gynecology has indicated that estrogen is the first-line therapy for the prevention of osteoporosis. When estrogen is contra-indicated, alternatives to estrogen can help prevent and treat bone loss (osteopenia and osteoporosis) of the spine, hip and total body. Refer to my article entitled **Osteoporosis** for further discussion and options for treatment.

Benefits and Risks of Estrogen

A. Breast Cancer

The majority of women still believe that breast cancer is the leading cause of death in the United States for women aged 65 years and older. In reality it is responsible for less than 4% of deaths. The risk for invasive breast cancer increases with age and with a positive family history. For woman in their 90's the incidence approaches 12%. Importantly, however, is that early detection of breast cancer has resulted in a cure rate of over 95% in women. The long-term follow-up of the women in the WHI study indicates an actual statistical decrease in the risk of breast cancer in those who were on ERT for over 20 years. Further, in those women who did develop breast cancer and used ERT there was a 63% higher survival rate than those women who had not used estrogen.

B. Cancer of the Uterus (Endometrium):

The lifetime risk of cancer of the endometrium in a woman reaching the age of 85 and who is not taking estrogen is 2.7 percent. Studies have shown that women who take estrogen alone have up to a three-fold increased risk of developing endometrial cancer. If progesterone is combined with the estrogen, there is no increased risk. Since patients who are on ERT or HRT are closely monitored by their physicians, any potential abnormality is usually found before it becomes an actual cancer. If a woman has had a hysterectomy, there is no risk. Further, studies have demonstrated that the use of birth control pills during the reproductive period of a woman's life decreases the risk of endometrial cancer by about 50% for 15 yrs. after stopping the pill.

C. 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 85, fewer than two would get ovarian cancer. In comparison, 12 women would get breast cancer, and 32 would develop osteoporosis. The WHI study did not find any increased risk in ovarian cancer. Studies do suggest that the use of birth control pills during the reproductive years decreases the risk of cancer of the ovary by 40 - 80%, and this decrease persists for at least 15 yrs. after discontinuance of the pill.

Currently, there are no specific screening tests for ovarian cancer. A blood test called a CA-125 is used as a tumor "marker" in a woman who has been previously treated for ovarian cancer. Ova-1 is a blood-screening test used in patients at risk for ovarian cancer. These are not *routine* screening tests. Neither are they specific for cancer, as the CA-125 may be elevated from other diseases, and it may be normal in the presence of early cancer of the ovary. Early detection of ovarian cancer is most frequently found by pelvic ultrasound.

D. Blood Clots

Blood clots in the veins are called *venous thrombosis*. If the clot becomes dislodged and travels to the lungs, the condition is called *venous thrombo-embolism* or VTE and can be fatal. The initial results of the WHI study showed a slight increased risk with estrogen alone and a slightly higher risk with progesterone. However, the follow-up review of the WHI did not show any increased risk in women who only used estrogen. Further, multiple studies have established that there is no increased risk of blood clots, when estrogen is given by a *non-oral route* described above.

E. Heart Attack and Stroke

After menopause the risk of heart disease and stroke slowly increases and by the age of 60 the risk equals that of men. This increasing risk is attributed to the loss of the beneficial effects of estrogen on cholesterol levels, distribution of body fat, blood coagulation, insulin sensitivity and a decrease of in the health of the arterial walls. This increased risk is not present in women who begin ERT in the early phase of their menopause. The initial and long-term follow-up results of the WHI study showed a decreased incidence of heart attack in the estrogen alone group. Women who took estrogen for at least 5 years had a 64% reduction in their coronary artery calcium score.

Further, both the estrogen and the estrogen-progesterone studies reported a significant reduction in new cases of diabetes. More than 40 years of clinical trials and observational studies have reported on the cardiovascular protection from estrogen usage in post-menopausal women. The recent prospective study (Ref. #26) demonstrated a 50% reduction of cardiovascular disease events (heart attack, heart failure and stroke).

F. Cognition, Dementia and Alzheimer's Disease (See Update below)

Cognitive decline is a nearly universal feature of aging. Starting at age 55, the hippocampus (the region in the brain critical to memory formation) shrinks 1 to 2 percent every year. It is estimated that 1 in 9 people age 65 and older has Alzheimer's disease. This number is expected to grow rapidly as the baby boom generation ages. The brain has remarkable neuroplasticity; that is, it can *remodel* and change itself in response to various experiences. Studies have demonstrated that memory training helps older subjects improve verbal reasoning. Further, physical exercise can also improve cognitive function and promote the creation and growth of neurons and new synaptic pathways for learning. A study was presented at the 2015 Alzheimer's Association International Conference held in Washington, D.C., which demonstrated that elderly patients with mild cognitive impairment (MCI) who completed a 12-week multidisciplinary brain fitness program saw marked improvement in cognitive performance and enlargement in the size of the hippocampus. Key parts of this program included neuro-feedback, meditation, exercise, dietary changes and omega-3 fatty acids. The role of diet in being heart healthy is also going to be brain healthy.

Numerous studies have reported that estrogen therapy started early in the menopause period reduces short-term memory loss, improves cognitive thinking, and reduces the long-term risk of dementia and Alzheimer's disease, especially when used long term (over 10 years). Studies also show that it is not necessarily protective when estrogen is started in women 15 years or more after menopause. A recent study from the University of Guelph, Ontario, Canada demonstrated that in female mouse brains infusion of estrogen caused an immediate increase in brain cell synapses (connections) located within the hippocampus. It further showed that these new connections remain silent unless they are used for learning. Learning tasks strengthened the connections, e.g. 'Use it or Lose it'. (Ref. #28-35)

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*Alzheimer Disease (AD) is the most common form of dementia, and it affects women more than men. One factor explaining this higher prevalence is that women have a longer life expectancy. A second factor may be the decline in estrogen that occurs with menopause. A recent prospective study published in 2017 showed a significant reduction in AD with hormone therapy. During a 20-year period, Finnish investigators sent questionnaires every 5 years to all women in their 40s and 50s who resided in a single province. National registry data was used to identify cases of AD. Among this cohort of over 8000 women, AD was diagnosed in 227 women. Although any use of hormone therapy (HT) was associated with a lower risk for AD compared with no use, this difference did not achieve statistical significance. However, **if** more than 10 years of HT was used, there was an associated statistically significant 40%-50% reduction in the incidence of AD.^[36]*

The findings of this Finnish population-based, prospective cohort study are congruent with those of a US study^[37] that was conducted in a single county (Cache County) in Utah and used similar methodology. This study also reported that if initiated within 5 years of menopause and continued for more than 10 years, HT was associated with a reduced risk for AD.

The timing or 'critical window' hypothesis proposes that HT exerts beneficial effects when initiated soon after menopause. Recent trials, including the Women's Health Initiative^[38] and ELITE,^[39] have provided evidence strongly supporting this timing hypothesis with respect to coronary heart disease and estrogen therapy.

G. Longevity

Current evidence indicates that when estrogen therapy is started early and continued for over 20 years, women have a 60% overall lower mortality rate, primarily from a reduced incidence of heart attacks, stroke and complications from osteoporosis.

Alternative Therapies in the Management of Menopause

For many women concerns about taking estrogen prompt them to rely on ‘natural’ alternative medicines to improve or control their symptoms. Estradiol is the primary estrogen produced during the reproductive-aged women. *Phytoestrogens* are naturally occurring in plant substrates and are functionally similar to a weak form of estradiol. It is important to recognize that all steroid hormones are derived from three major plant sources: soybeans, Chinese cactus needles and Mexican yams, with the exception of conjugated estrogens (Premarin and Cenestin). Therefore, these products are all natural. The issue with over-the-counter remedies is the absence of any quality or potency control. These ‘natural’ products are completely unregulated regarding their safety. Further, there are no reliable studies that have demonstrated that these alleged remedies for mild symptoms are giving any protection for the tissues discussed previously.

The following is a list of supplements that may help with the milder symptoms of menopause:

1. Black Cohosh: hot flashes, night sweats
2. Red Clover: hot flashes, night sweats
3. Phytoestrogens (soy and flaxseed products): hot flashes, night sweats, and vaginal dryness.
4. St. John’s Wort: mild depression

Remember: Alternative therapies provide no benefit for vaginal thinning (causing dryness and pain with intercourse) or osteoporosis prevention. Although these supplements generally do not appear to stimulate the endometrial lining of the uterus and should not cause vaginal bleeding, patients using supplements or phytoestrogens must inform their physician so they may be properly monitored.

SUMMARY

- ❖ Menopause is a natural phenomenon that occurs in all women when their ovaries cease functioning.
- ❖ Absence of ovarian function results in a loss of circulating estrogen, progesterone and testosterone that can cause physical, emotional and mental changes and symptoms. The absence of estrogen will result in certain reversible and irreversible physical changes and increased risks as discussed in this article.
- ❖ Estrogen is important to the emotional, mental and physical well-being of a woman’s life after menopause.
- ❖ ERT and HRT have statistically been shown to be safe and protective after 20 years of use.

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