Women's Wellness Center
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Peri-menopause and Hormone Health

An important decision every woman must make is whether or not to use hormone replacement therapy (HT) after menopause. As a physician specializing in women's health, it concerns me that so many people today have profound misunderstandings regarding the safety and benefits of HT. If you are suffering the effects of hormone loss, you should know that relief is safe and available. Whether you choose to use hormones or not, your decision should be based on facts, not misinformation, misconceptions, or fear.

What is menopause and peri-menopause?

Menopause marks the cessation of ovarian hormone production, on average between age 48 and 52. Ovarian hormones (the sex hormones: estradiol, testosterone, and progesterone) are involved in countless bodily functions, not just reproduction. Hormone depletion triggers changes that negatively affect both quality of life and long-term health. Regarding quality of life, symptoms often experienced during (and long after) the menopausal transition are hot flashes, night sweats, sleep disturbance, depression, irritability, anxiety, brain fog, low libido, vaginal dryness, and bladder symptoms. Less common symptoms are heart palpitations, dizziness, and itchy-crawly skin, dry eyes, and burning sensation of the mouth. Regarding long-term health, the menopause transition brings physiologic changes that accelerate inflammation and diseases of aging, like heart disease, osteoporosis, and dementia.

Peri-menopause includes several years preceding menopause, when women often begin having bleeding problems and symptoms noted above. Being proactive with hormonal evaluation at the peri-menopause stage can help mitigate impact on quality of life and degenerative bodily changes soon to come.

The Menopausal Transition: A Natural Part of Life

If menopause is a natural part of life, isn't it unnatural to supplement hormones after they are depleted? Truly, what is *unnatural* is humans living 80 years or more. As recently as 100 years ago, most women did not live beyond the age of 50, the age that approximately coincides with natural ovarian failure and hormone depletion. Now, female life expectancy is 80 to 81 years, because in this era we have the benefit of effective medical technologies such as antibiotics and other medications to prolong life. Women live anywhere from a third to a half of their life in a hormonally depleted state. Most people do not question whether to take a thyroid supplement when thyroid function is deficient, insulin when pancreatic production is deficient, or whether to use antibiotics to treat an infection that would otherwise be life threatening. Why would we agree to take advantage of these interventions throughout life, yet choose not to replace our critically important sex hormones with formulations that are chemically bioidentical, *molecularly identical to our depleted hormones?*

What do our natural hormones do for us?

- **Estradiol** is key in controlling the menstrual cycle, fertility, and pregnancy. This hormone also plays a critical role in many bodily functions, evidenced by abundant estradiol receptors in your heart, brain, bones, joints, skin, eyes, teeth, gums, nerves, blood vessels, urinary tract, reproductive organs, and more. So, the loss of estradiol may be suffered in countless ways.
- **Testosterone,** often considered a "male hormone" is a vital hormone in women, eliciting physiologic effects through androgen receptors in almost all female body tissues, including breast, heart, blood vessels, intestines, lungs, brain, spinal cord, nerves, bladder, uterus, ovaries, endocrine glands, vaginal tissue, skin, bone, joints, and fatty tissue, and

more. Testosterone is actually the most abundant sex hormone in a woman's body. Yes, you read that correctly – females produce many times more testosterone than estrogen. We need to pay attention when it's depleted.

- **Progesterone**, during the reproductive years, is responsible for supporting and maintaining pregnancy, and throughout life it is important to have progesterone to balance the effects of estrogen in your body.

What are benefits of hormone therapy after menopause?

- **Benefits of Estrogen Therapy**. The most obvious and immediate benefit of this extremely well-studied therapy is the relief of mild to severe symptoms resulting from hormonal decline. However, when ovarian hormones decline it also brings changes that set the stage for chronic disease. Timely replenishment of sex hormones lowers risk of these and other conditions related to aging. Table 1 below lists some of the documented benefits of estrogen therapy.

Table 1. Well-Documented Benefits of Estrogen Therapy after Menopause

- Estrogen is the most effective treatment for symptoms of menopause - hot flashes, night sweats, sleep disturbance, depression, irritability, anxiety, brain fog, low libido, vaginal dryness, and bladder symptoms.
- If begun within 10 years of menopause onset, estrogen lowers risk of cardiovascular disease by 40-50% through a beneficial effect on cholesterol levels, decreased plaque formation in the coronary arteries, vasodilation, and anti-inflammatory properties. Cardiovascular disease is the most common cause of death in postmenopausal women.
- Evidence suggests estrogen therapy decreases risk of diabetes in postmenopausal women.
- Estrogen replacement reduces osteoporosis by 50%. The mortality rate of osteoporotic hip fracture after age 75 is 50%. Without estrogen replacement there is a steep decline in bone density over several years. If ongoing estrogen therapy is stopped, bone density declines rapidly, and will become as poor as if estrogen therapy had never been used.
- Estrogen therapy protects the brain. If initiated early and continued long term, estrogen has been shown to decrease incidence by 70%, neurodegenerative diseases such as Alzheimer's Dementia and Parkinson's Disease. If estrogen replacement is discontinued, that brain protection is lost.
- Estrogen therapy lowers by 50% colon cancer, which carries a mortality rate second only to lung cancer.
- Estrogen replacement decreases risk of macular degeneration, the most common cause of vision loss and blindness in adults over 65 years of age. Estrogen also lowers incidence of cataracts.
- Estrogen therapy helps prevent degenerative arthritis, and also reduces tooth loss.
- Estrogen replacement helps to preserve or restore healthy sexual functioning, including vaginal health, maintenance of healthy sexual desire, and ability to achieve orgasm.
- Estrogen preserves skin tone, reducing formation of wrinkles through positive effects on collagen.

- **Benefits of Testosterone Therapy.** Testosterone has been largely ignored as an essential hormone in female physiology. This is unfortunate, since women often begin to experience adverse effects related to testosterone decline well before those associated with the fall in estrogen. In a woman's body, production of testosterone peaks in her mid 20's and begins to steadily decline, down to about 50% by age 40. This is when a woman will often present with complaints such as increased abdominal fat, hair loss, fatigue, brain fog, loss of sex drive, reduced orgasm, anxiety, irritability, depression, headaches, joint/muscle pain, and general lack of well-being. We may attribute these symptoms to the inevitable decline of vigor with aging, but by recognizing these changes as a signal alerting us to a state of hormone depletion, we can improve physical health and vitality as we enter mid life.

  Testosterone replacement for symptomatic women has the potential to improve mood, libido, orgasm, energy level, lean body mass; to relieve muscle and joint aches; and to promote a general feeling of well-being. In addition, potential health benefits include reduced cardiac risk, improved bone density, and there are studies suggesting a favorable effect on brain and breast health. Testosterone therapy can be beneficial for symptomatic individuals as early as a decade or more before onset of the menopausal transition.

- **Benefits of Progesterone Therapy**. This hormone is often important to balance the effects of estrogen in the body. For example, when the uterine lining (endometrium) is exposed to estrogen, either naturally produced by the body,

or as a supplement, it responds by thickening and growth. If this were to occur without the balancing effect of progesterone, the endometrium would continue to grow and thicken without limit, leading to increased risk of endometrial cancer. In addition to its uterine protective role, progesterone supplementation also helps relieve symptoms, such as anxiety and sleeplessness. Some researchers have suggested that bio-identical progesterone supplementation may offer protection against breast cancer, and while this has not been firmly established, studies have shown that bio-identical progesterone is very safe with regard to breast health.

What are side effects of HT?

- **Estradiol**. The vast majority of women using HT have relief of symptoms with no side effects. Of those who report side effects, the most common are transient breast tenderness and uterine bleeding. Both of these are usually limited to the first few weeks after initiation of treatment. If bleeding is persistent, there are several non-surgical solutions for controlling it. Weight gain, while inevitable in the midlife physiology of aging, is not a side effect of HT.
- **Testosterone**. Testosterone therapy is well tolerated; the majority of women report no side effects. A small number will experience facial hair or acne, both of which can be managed by reducing the dose or a medication that blocks testosterone effects on the skin. Often, women who experience these side effects prefer to manage the issue rather than reduce their dose, a testament to their satisfaction with therapeutic benefits received.
- **Progesterone**. Progesterone taken orally can make one sleepy. Most women who take progesterone at bedtime welcome and enjoy a good night's sleep and don't feel sleepy the next day. A small number are more sensitive to the side effect of sleepiness with oral progesterone, and it may be preferable to use a different formulation.

Is there any safety concern with use of HT?

- **Estradiol Safety**. Only when taken as an oral pill, estrogen slightly increases risk of blood clots, which can lead to thrombosis, stroke, or pulmonary embolism. This is because after the tablet hormone is absorbed by the stomach, it is transported directly to the liver, where extensive metabolism leads to increased production of blood clotting and inflammatory factors. Research has shown that when estradiol is absorbed slowly (via patch, topical cream, or subcutaneous pellet) there is not elevated risk of blood clot/inflammation because the hormone is delivered gradually into the bloodstream through capillaries, rather than first passing through the liver all at once. For the same reason, oral estrogen slightly increases the risk of gall bladder disease, also avoided with use of transdermal or subcutaneous pellet therapy. Bottom line: The safe way to receive estradiol supplementation is by a non-oral route.
- **Testosterone Safety**. Bio-identical testosterone for women has been used off-label for decades, and there is a growing body of data regarding its safety for hormone replacement. Any adverse health risk you may have seen referenced would likely be related to the synthetic pill methyltestosterone, which is subject to the first pass liver effect described above. Unfortunately, when disease risk related to hormone therapy is reported, authors commonly lump all hormones into one pile, seemingly not recognizing that synthetic formulations are often more potent, not biochemically identical to each other or to our natural hormones, and have different effects on the body than our natural hormones. Current data specifically regarding bio-identical testosterone formulations in women have not shown increased risk in cancer, cardiovascular disease, or other serious condition.
- **Progesterone Safety**. When used appropriately as directed, there is no known medical or clinical risk of using bio-identical progesterone, by oral or other route of delivery. Anyone who mentions risk associated with progesterone therapy is confusing it with a synthetic progestin, such as Provera (medroxyprogesterone) or norethindrone, which have been associated with cardiovascular risk.

Does HT increase risk of cancer?

The only cancer conclusively demonstrated to increase with estrogen therapy is uterine cancer, and the proper use of progesterone eliminates the increase in uterine cancer. Use of unopposed estrogen can cause over-stimulation of the cells of the uterine lining, but when properly balanced with progesterone, uterine lining growth is limited, and there is no increase in uterine cancer risk.

The perceived risk of HT that draws the most attention is concern of its link to breast cancer. However, dozens of studies have examined estrogen therapy and breast cancer, and though some suggest a very small increase in risk, many more

show no increase, and a few show a decrease in breast cancer for women using HT. Some reports suggest that a pre-existing breast cancer will grow in response to estrogen, but this is not proven. Even if true, it does not follow that estrogen caused the breast cancer. The fact is, scientists have studied hormone therapy for decades, and there is not conclusive evidence that HT directly contributes to development of breast cancer. See the box below for more discussion of breast cancer and HT.

Does HT increase risk of heart disease?

In 2002, the Women's Health Initiative, or WHI study (see box below), reported increases in cardiovascular events with HT. However, closer analysis of the WHI data brought to light a crucial fact: the timing of initiation of HT is key, and it is most beneficial to initiate HT early in the menopause transition, before artery-clogging plaques begin to develop in the heart. This benefit has been demonstrated in dozens of studies throughout the past several decades.

The WHI Study: A Pivotal Point in the History of Hormone Therapy

Why the Controversy?

If HT has so many benefits, what explains the prevailing view that it's dangerous? By the late 1990's, it had become standard medical practice to recommend HT after menopause, due to copious data supporting its benefit to heart, brain, and bone, plus relieving menopause symptoms. Then came a study called the Women's Health Initiative (WHI) in 2002. The investigators rushed a press conference to announce findings even before the study had been published in a medical journal, a serious breach in scientific procedure that put headlines across the globe before the scientific community had a chance to weigh in. WHI reports claimed HT increased the risk of breast cancer, cardiovascular disease, and dementia, alarming the public and health professionals alike, ultimately leading to a sharp decline in use of HT. The study was touted as the largest to date, and being a randomized controlled trial, should be of superior reliability. However, a study is only as good as its design, and after publication, with close analysis, numerous critical flaws in the WHI study have been revealed.

Breast Cancer Concern

Initial reports of findings were designed for maximum impact, claiming that HT increased breast cancer by 26%. That sounds like a lot of extra cases of cancer, but in absolute numbers means an increase of only 8 women in 10,000 – less than one case per 1000 women per year. This difference actually *does not reach statistical significance* as understood in standard scientific method, yet media reports did not disclose this crucial point. Even more egregious, careful analysis of the data reveals there was not really an increase in breast cancer for the HT users in the study, but rather a lower incidence than expected in the control group (HT nonusers). A testament to the benefit of HT was revealed when it was recognized that many in the control group had a history of HT use prior to entering the study (that in itself a grievous flaw in study design), and when these subjects were removed from the data pool, the difference in breast cancer vanished, suggesting that prior hormone use may have been protective. Where was the press conference when this finding was released?

Heart Attack Alarm

Reporting of heart disease risk was bungled in a different way. WHI claimed an increase in heart attack and stroke for those on HT. However, it was only the older patients in the study, aged 60-79, who had increased cardiac disease, and they likely had pre-existing disease. Younger subjects starting HT around the time of the menopausal transition, aged 50-59, had *less* heart attack and stroke with HT compared to no HT. This age stratified analysis of the data, reported several years after the initial negative findings, did not receive the heavy media attention of the early negative reports. To this day there are still cardiologists and other doctors who believe HT is dangerous based on one poorly designed (but very loud) WHI study.

Dementia Debate

Another shocking claim of the WHI was that dementia increased in postmenopausal HT users. This was another surprise to the medical community, because there had previously been numerous clinical studies showing just the opposite, that HT protects the brain from dementia. Close scrutiny of WHI data reveals that only the subjects who were 75 or older developed dementia, and when investigators excluded subjects that already had mild cognitive impairment upon entering the study, the difference was not statistically significant. Women in the study who received HT starting in their 50's had less incidence of dementia than nonusers. Moreover, those who'd used HT close to menopause, prior to entering the study, had 50% lower risk of dementia and all neurodegenerative diseases. Again, early initiation of HT is key for prevention of disease.

The Bottom Line

Poor design and irresponsible reporting of the WHI is why misunderstandings exist regarding safety of HT. Truly, it was a mistake of monumental proportions for the WHI investigators to report an increase in breast cancer, heart disease, and Alzheimer's dementia for HT users. It is astonishing how persistent early misconceptions can be, and thus how pervasive the fear of HT has become. It is an absolute tragedy for millions of women who have been denied the benefits of HT.

Is it safe to start HT several years after menopause?

HT is safe and beneficial for relieving symptoms, even if initiated long after the menopausal transition. However, the preventative potential regarding heart disease, bone loss, and Alzheimer's are optimized if HT is initiated within 10 years of menopause. Some studies suggest initiation of HT more than 10 years after menopause could slightly increase risk of a cardiovascular event within the first year of HT use; and after the first year risk drops to the same as HT nonusers.

How long should HT be continued?

The fact is, when HT is discontinued, the body is susceptible to all the conditions/symptoms that HT had been preventing/controlling for the duration of HT use. Before WHI, hormone therapy was routinely encouraged for symptom control and for benefits on heart, brain, and bone health. After WHI, we began to see the admonition: "If hormone therapy is prescribed, it should be used in the lowest dose, for the shortest time possible." In the 2 decades since WHI, its data having been scrutinized and found wanting, we have come full circle. The North American Menopause Society (NAMS), in a 2017 position statement, noted that "hormone therapy does not need to be routinely discontinued in women older than 65… There are no data to support routine discontinuation in women age 65 years."

What hormone delivery method is best?

The method chosen depends upon one's individual preferences, convenience and cost. Some are clinically superior.

- **Subcutaneous Implant.** Hormonal implant is a favorable delivery method that avoids the risk associated with liver first-pass effect, discussed earlier. A minor office procedure inserts tiny pellets consisting of bioidentical estradiol and/or testosterone just beneath the skin of the upper buttock. The implants deliver hormones gradually, and over several months are completely absorbed. Hormone implant therapy is a safe, convenient and efficient way to receive HT, providing steady relief of symptoms without having to think about it on a daily basis.
- **Transdermal (Patch, Cream, Gel).** Delivery of estradiol and testosterone via transdermal absorption (through the skin), avoids the first-pass liver effect. Transdermal hormone delivery results in steadier hormone levels throughout the day compared to pills.
- **Vaginal Application.** Vaginal application of hormones (cream, tablet, or suppository) can be extremely beneficial for vaginal dryness and painful intercourse, as it replenishes blood supply, moisture, tissue integrity and elasticity. It is also beneficial for bladder health, improving symptoms of urinary urgency or frequency.
- **Sublingual or Buccal Delivery.** Hormones supplied as sublingual or buccal troches dissolve and deliver hormone into circulation from oral tissues. Some of the hormone may be swallowed and absorbed into the gut; this is negligible if troches are used correctly. Rapid oral absorption produces early peak levels, so 2-3 doses per day may be required.
- **Injection.** Intramuscular injection of hormones is discouraged for a number of reasons. It provides less reliable symptom relief, and side effects are more likely. A significant drawback, besides the inconvenience of a shot every 1-2 weeks, is the highly variable levels of hormones in the blood, a roller coaster of hormone excess and deficiency. We advocate methods that provide more consistent hormone levels, thus consistent control of symptoms.
- **Progesterone Delivery: Oral, Vaginal, or Intrauterine Device (IUD).** Progesterone is often given as an oral formulation, as dosing is convenient and absorption reliable. Oral progesterone does undergo first-pass liver metabolism, but instead of producing harmful factors in response, the liver produces metabolites that act on the brain to induce a state of calm, or even sleepiness. This is a therapeutic side effect of oral progesterone, and is why we recommend taking it at bedtime. Other favorable methods are progesterone vaginal suppositories or a progestin IUD such as *Mirena*. Progesterone creams can treat certain symptoms, however, progesterone is not absorbed through the skin in sufficient levels to counter estradiol's proliferative effects on the uterine lining.

Does menopause affect thyroid health?

It is natural for thyroid hormone production to decrease gradually with age. Some of the symptoms of peri-menopause can overlap with symptoms of low thyroid hormone. Fatigue, depression, sleep disturbance, low libido, brain fog, decreased mental sharpness, and weight concerns are common with thyroid hormone deficiency. Replacement of low or borderline-low thyroid hormone can make a dramatic difference in quality of life.

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