justifying female hormone replacement therapy

Navigating the world of hormone replacement (HRT) is no easy task. With the massive expanse of research on the topic it seems odd that there is still such a lack of consensus among health care practitioners. Despite the continuous controversy, we choose to err on the side of our patient's well-being and stand quite strongly for the intelligent replacement of sex hormones. As your provider, I wanted to make the effort to explain my position on HRT and why we believe the majority of the controversy to be poor science.

The Women's Health Initiative (WHI) was a public health undertaking to investigate the safety of using horse derived estrogen alone, and in combination with the synthetic progestin medroxyprogesterone (not progesterone, by the way). However, the study was terminated early because the authors found a "significant increase in breast cancer" (a relative 26% and absolute 1% increase) and that continuing the study would have been unethical. Consequently, the demonization of HRT began. Fast forward a few years and the data were refuted, discarded, and ignored as scientists came forward with conflicting data suggestive of quite the opposite – reduction in breast cancer risk. Not only that, but HRT was actually associated with reduction in all-cause mortality, which means an increase in lifespan. The WHI was finally retracted when the studies began to report positive benefit to HRT in realms outside of cancer, which is important when you look at the leading cause of death in women – heart disease.

In the U.S, 1-in-4 (25%) women die of heart disease, where the lifetime risk of dying from breast cancer is 1-in-38 (2.6%). So, women are 10 times more likely to die from heart disease than breast cancer. Looking even further, the risk of developing breast cancer is about 12%, whereas the risk of developing heart disease is about 56%. This becomes relevant when HRT reduces the risk of heart disease by 40%. So, even if the tiny increased risk in breast cancer from HRT per the WHI did exist, the relative decrease in risk for heart disease would have a much higher impact on longevity – in addition to the increased quality of life that women on HRT experience. In 2017, a final piece came out in the Journal of the American Medical Association (JAMA) that conducted a mortality analysis for the entire study and follow up data that concluded no increased risk of all-cause, cancer, or cardiovascular mortality.

summary of the problems of the WHI methodology:

- **the study participants:**
- average age was 63 (average age of menopause is 50) – only 30% of participants were between 50-59
- 70% were very overweight or obese
- >50% were smokers
- many had hypertension or other co-morbid conditions
  (women who were especially symptomatic of menopause symptoms were excluded)

The French E3N study was an 80,000+ cohort of teachers and teacher's wives aged 40-65 that began in 1990. This prospective study gathered data on hormonal status (menopausal or not) and use of HRT, among many other categories. Retrospective analysis of the data has since provided evidence to support that transdermal estradiol in combination with oral micronized progesterone does not increase the risk of breast cancer, whereas the use of the transdermal estradiol alone or with various different synthetic progestins all increased the risk of developing invasive breast cancer. Additionally, there is no increased risk for venous thromboembolism (blood clot), stroke, or gallbladder disease with this combination, either. While it is important to remember that association is not equivalent to causation, from an evidence-based perspective the combined use of transdermal estradiol and oral progesterone seems to confer the greatest benefit with the least amount of risk.

Wisdom and common sense would indicate that employing lifestyle changes to support an artificial 'return to youth' is vital to intelligent practice. This is why we always run comprehensive blood work, inquire about diet, sleep, and exercise, and devise plans to address those areas as we begin HRT. Estrogen, progesterone, DHEA, and testosterone all have various benefits to women's well-being and that is why we believe in utilizing them. Importantly, it should be remembered that, generally, the healthiest years of life are during the years of sexual maturity characterized by the pulsatile rhythms of the endocrine system. In a time where we have collectively pushed the limits of longevity past reproductive years, we are of the belief that the physiology must be supported to maintain well-being.

summary of benefits:

estrogen benefits:

- cardiovascular benefits
- vascular endothelial cells Increases vasodilation and cell migration.
- this translates to increased blood flow, oxygen delivery, and cell homing.

- smooth muscle cells
- decreases proliferation and cell migration.
- this translates to a reduction in abnormal smooth muscle remodeling that surrounds atherosclerosis, pathogenic blood vessel growth, and tumor growth.

- cardiomyocyte
- reduces LDL oxidation, insulin resistance, and hypertrophy.
- this translates to reduced cardiovascular disease risk.

bone benefits:

- increases the production of calcitonin, thus inhibiting bone resorption.
- accelerates calcium resorption by the intestine.
- reduces the calcium excretion from the kidney.
- direct binding to estrogen receptors on bone.
- decreases risk of fracture by 50%.

cognitive benefits:

- Frontal and hippocampal cortices are heavy in estrogen receptors (ERs) These areas are vital in personality, emotions, motivation, exploration, learning, memory, and mental abstraction.
- Enhances dendritic remodeling and plasticity by increasing neurotropic factors.
- Brain neurotrophic factors decrease with age and can be linked to mitochondrial dysfunction across the whole brain.
- Increases cerebral blood flow, which means more oxygen and more potential fro energy flux in the brain.
- 20-50 + % decrease in risk for dementia.

progesterone benefits:

cognitive benefits:

- Greatly neuroprotective
- Enhances long-term potentiation (mechanism for learning) in hippocampus
- Decreases glutamate toxicity by increasing brain-derived neurotrophic factor (BDNF). Progestin does the opposite.
- Stabilizes mitochondrial membrane and prevents mitochondrial transition pore opening and cytochrome C (CytC) release. (this translates to better energy production and less cell death with age.)
- Has affinity for GABAa receptor domain, as does its metabolite allopregnanolone.This translates to decreased anxiety, depression, and better parasympathetic balance.
- Neurons have membrane progesterone receptors that are involved in numerous aspects of cell function, ranging from neuronal development, steroidogenesis, regulation of cerebrospinal fluid (CSF) production and osmoregulation, and the regulation of reproductive behavior.

estrogen governacne:

- Downregulates ERs in the breast and also binds ERs to antagonize.
- Induces programmed cell death (apoptosis) in breast cancer cells.
- painful uterine contractions of primary dysmenorrhea are mainly caused by an increased mucosal production of porstaglandin stimulated by estradiol and attenuated by progesterone.

testosterone governance:

- cancer
- Decreases breast cell proliferation, however aromatization can reverse this benefit.
- Given with aromatase inhibitor can reduce risk of breast cancer, assuming estrogen is abnormally elevated.
- Cardiovascular Benefits:Improves endothelial function and increases coronary blood flow.

- musculoskeletal benefits
- Testosterone is an anabolic hormone that directly increases muscle strength and bone health while burning fat from internal stores and also fighting the deposition of new fat.

- sexual health
- While by no means a panacea for libido, adequate testosterone seems necessary to maintain desire and sexual function.

a blurb on the differences between progestins and progesterone

Though both progesterone and the synthetic progestins can fit the lock of the classical progesterone receptor, it is important to recognize that there are important pharmacological (events that occur after receptor binding) and pharmacokinetic (how the compound is metabolized and excreted) differences between the two. From a pharmacokinetic perspective, orally administered progestin, like in oral contraception, does not undergo any first pass effects in the liver, unlike progesterone. Furthermore, progestin's affinity for sex hormone binding globulin is very low. This leads to higher blood concentrations after taking the progestin and thus a higher likelihood of receptor stimulation. In addition to differences in bioavailability and half-life, progestins also display many effects that progesterone does not, including the ability to bind to the androgen receptor (AR) where they may act as a partial activator. Progesterone, in contrast, does not bind to the AR. Progestins can also bind to, and activate, glucocorticoid (i.e. cortisol) receptors with an effective concentration that is nearly 300-fold lower than that for progesterone.

While progesterone and progestins may be equally effective at reducing uterine tissue proliferation, their effects on the brain are far from identical. In fact, it has become increasingly clear that while progesterone is neuroprotective, progestins are not. Specifically, while progesterone increases both the mRNA and protein levels of brain-derived neurotrophic factor (BDNF) in the cerebral cortex, progestin treatment resulted in a substantial inhibition. Combined with the observation that progesterone's protective effects may be dependent on neurotrophic signaling, this inhibition of BDNF expression by progestins may not just be without effect, but may actually have adverse consequences to brain function.
Progesterone's neuroprotective effects are also seen in the reduction of glutamate excitotoxicity that occurs in concussion, infection, developmental disorders, etc. In this context, progestin not only failed to elicit protective effects, but also blocked the beneficial effect of estradiol. Furthermore, some of the neuroprotective effects of progesterone are mediated by its neuroactive metabolite, allopregnanolone, and progestins are not converted to allopregnanolone. In fact, the neuroprotective effects of allopregnanolone are so profound that the FDA just recently cleared a drug that is a derivative of allopregnanolone for the treatment of post-partum depression.