Hysterectomy & Progesterone

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Does a woman without a uterus need a progestin if she's taking estrogen?

No, but she does need progesterone.

Since the late 1970s it has been the standard of medical care in the U.S. to prescribe a progestin along with estrogen for all women using hormone replacement therapy (HRT), except those without a uterus. Women without a uterus may be prescribed estrogen-only HRT, or ERT. The evidence used to create this recommendation originates in the finding that women who used unopposed estrogen had a significantly higher risk of endometrial cancer. At the time this standard was established, research had not yet conclusively demonstrated that excess estrogen increases the risk of breast cancer, ovarian cancer, blood clots and stroke. The belief that it is safe for a woman without a uterus to use unopposed estrogen is also based on the assumption that the ovaries are intact and continue to make estrogen, progesterone and testosterone.

Although researchers had discovered in 1938 that estrogen could be extracted in large quantities from pregnant mares' urine, it was extremely costly to manufacture progesterone, which was extracted from animal organs, as well as the cholesterol in sheep's wool, cattle brains and livestock spinal cords.

In the 1940s, chemist Russell Marker discovered that progesterone could be extracted from wild Mexican yams relatively inexpensively, but when taken orally it broke down in the stomach before reaching tissues, so the primary delivery method was painful injections. Needless to say, the use of progesterone did not catch on.

In 1951 a pharmaceutical company researcher created the first synthetic progesterone, later dubbed a progestin, by altering the testosterone molecule in a way that gave it some properties of progesterone. This was followed by the development of numerous other progestins over the next decade that were used to create the first oral contraceptives. These potent progesterone-like compounds prevented pregnancy by blocking ovulation and thinning the lining of the endometrium. When the progestin was withdrawn, the endometrial lining would be shed. *(Watkins)*

When it was discovered that unopposed estrogen increases the risk of endometrial cancer, pharmaceutical researchers quickly realized that if progestins could cause the shedding of the endometrial lining, this might prevent endometrial cancer, which was caused, it was thought, by the buildup of the lining by constant exposure to estrogen and no menstrual cycles. In 1984 an FDA advisory committee made it official, by recommending that, for women with a uterus, a progestin be added to estrogen for at least seven days a month to prevent endometrial cancer. *(Watkins)*

Meanwhile, oral contraceptives had entered the marketplace in the late 1960s, including Depo-Provera, an injection of the progestin medroxyprogesterone acetate (Provera or MPA) that prevents pregnancy for three months. Although not FDA-approved for contraception until 1992, Depo-Provera was widely used off-label for that purpose. Research at the time showed that Depo-Provera caused significant bone loss and increased the risk of breast cancer and cervical cancer. *(Curtis et al)*

Despite these concerns about Depo-Provera, the combination of oral Provera and Premarin , quickly rose to the top in sales of hormone replacement therapy (HRT), even though progestins had never been FDA-approved for use by menopausal women. By the late 1990s, Premarin and Prempro accounted for 70% of the HRT market, and in 1998 Premarin became the number-one selling drug in America. The majority of women who walked into a doctor's office after the age of 50 were offered, and even encouraged, to use PremPro. *(Watkins)*

In spite of the popularity of PremPro, Premarin was the best-selling drug for a reason—many women could not tolerate the side effects of Provera, which include

breast tenderness, abnormal bleeding and spotting, cramps, lower backache, nausea, headache, dizziness, edema, acne, fatigue, moodiness, irritability and depression. *(Pub Med Health)* Gail Sheehy, author of the 1992 best-selling menopause book Silent Passage, reported that doctors advised women who could not tolerate Provera to have a hysterectomy so that they could use Premarin alone.

In the late 1990s an oral micronized progesterone was approved by the FDA for use in hormone replacement. The micronization of progesterone suspends the hormone in long chain fatty acids so that it survives stomach acid. However, some 80% of it is still lost in the first-pass effect in the liver, so 100 mg is needed to deliver a dose of 20 to 40 mg. *(Hargrove)*

Risks of Progestins

The risks of estrogen replacement therapy *(ERT)*, particularly the possible increased risk of breast and endometrial cancers, and stroke, have been known since the 1950s, but through the following decades pharmaceutical companies argued that the bone-building and cardiovascular benefits of estrogen outweighed the risks.

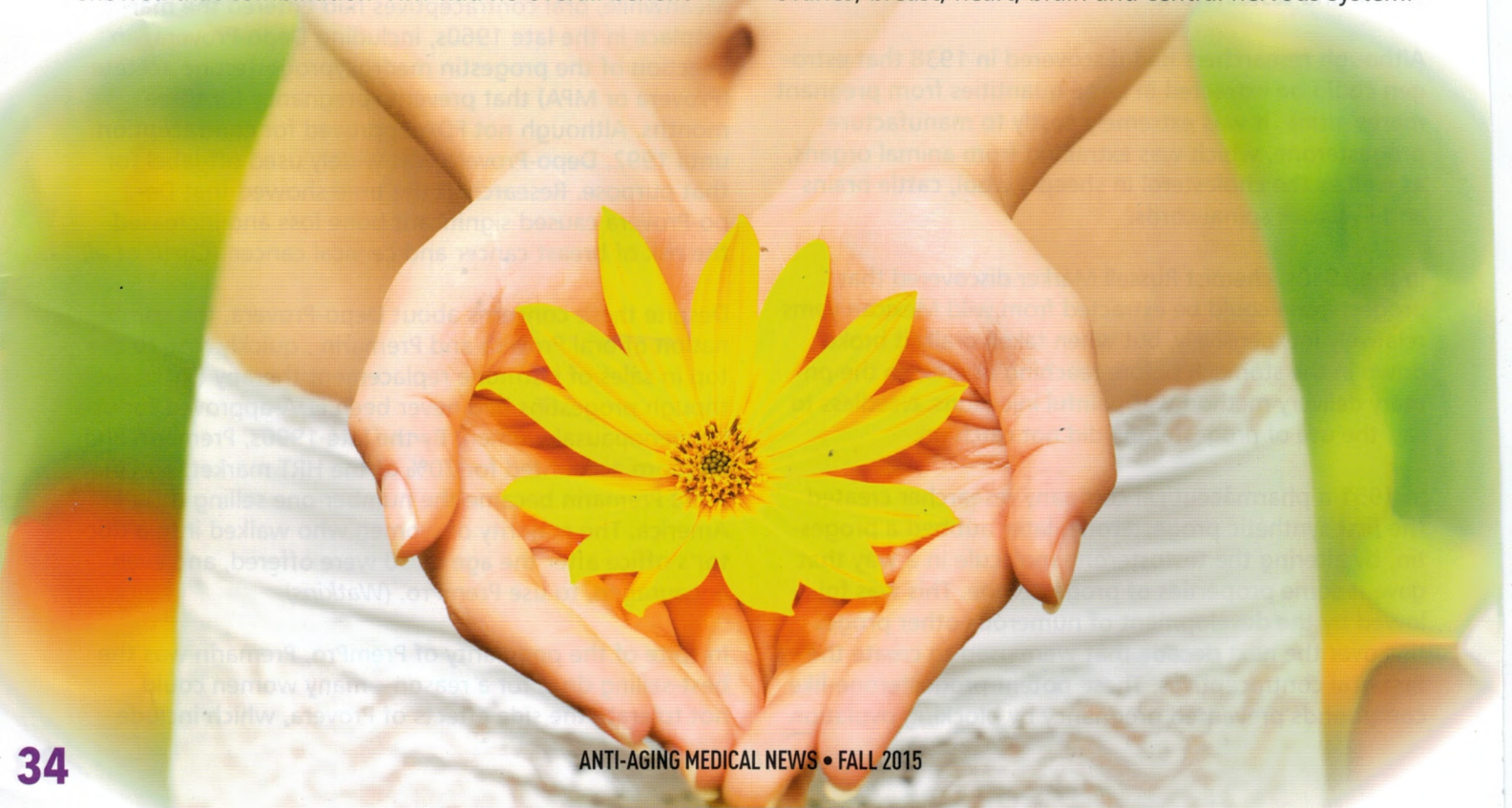
On the assumption that HRT would have the same benefits as ERT, HRT was heavily promoted for preventing heart disease. In 1985 the Framingham Heart Study found that HRT increased the risk of heart disease *(Wilson et al)*, but since the Nurses' Study results, released at the same time, showed benefit, the Framingham results were largely ignored. *(Stampfer et al)* In 1998 the gold standard double-blind, placebo-controlled HERs study showed that combination HRT had no overall benefit for heart disease and significantly increased the risk of thromboembolic events, but it was criticized for small size and again, largely ignored by doctors, who continued to prescribe HRT to the majority of their female patients over the age of 50. In 1997 research with Rhesus monkeys, *(Miyagawa et al)* found that medroxyprogesterone *(Provera or MPA)* induced coronary vasospasm, while progesterone did not. Finally in 2003 the Women's Health Initiative *(WHI)* data put an abrupt end to claims that estrogen-progestin HRT prevents heart disease. *(Manson et al)*

In the WHI estrogen plus progestin HRT increased the risk for probable dementia in postmenopausal women aged 65 years or older and did not prevent mild cognitive impairment. *(Shumaker et al)*

A plethora of research since the early 1990s has shown that progestins have multiple adverse effects and risks for menopausal women, including an increased risk of heart disease, thromboembolic disorders, breast cancer and gallbladder disease. When the Women's Health Initiative study released results in 2003 showing irrefutable evidence of these risks for PremPro users, HRT sales dropped by more than 60% within a matter of months.

The Effects of Unopposed Estrogen

While progestins protect the uterus from estrogen's risk of endometrial cancer, they do not oppose estrogen in other parts of the body, leaving women who use HRT exposed to the effects of unopposed estrogen on the ovaries, breast, heart, brain and central nervous system.



When assessing risks and benefits of estrogen, Premarin cannot be directly compared to estradiol. Premarin is extracted from pregnant mares' urine and is composed of a cocktail of hormones that includes progesterone and many of its metabolites, which likely play a role in opposing some of estrogen's tendency to stimulate cell division. Virtually all of the women in the WHI were using PremPro or Premarin.

The WHI study of hormone replacement had two arms: one for combined progestin and estrogen HRT *(PremPro)*, and one for estrogen-only *(Premarin)*. Within those two arms was a controlled trial with a placebo group, and an observational group.

The Premarin-only group were all hysterectomized, and many were also oophorectomized.
In 2007 the Premarin-only arm of the WHI was discontinued after seven years because of a significantly increased risk of stroke among Premarin users. In the controlled trial, Premarin users had a slightly lower risk of breast cancer than non-users, while the women in the observational group had a 28% increased risk of invasive breast cancer compared to nonusers. The authors of the WHI results attribute this difference to the controlled trial demographics, which included a large number of older women who had not previously used hormone therapy. They theorize that the menopausal breast undergoes epithelial changes which may help protect it from the cancer-promoting effects of estrogen. *(Prentice et al)*

Not long after the WHI estrogen-progestin trial was stopped, the Million Women study from the U.K. showed a 30% increase in breast cancer in women using estrogen-only hormone replacement. *(Beral et al 2003)*

Another arm of the Million Women study showed that women using unopposed estrogen had a 42% higher risk of central nervous system tumors, gliomas, meningiomas, and acoustic neuromas than non-users of hormone replacement. *(Beral et al 2007)*

Unopposed estrogen significantly increases the risk of ovarian cancer. The 1979-1998 cohort study of former participants in the Breast Cancer Detection Demonstration Project found a seven percent increase in the risk of ovarian cancer for every year of use of unopposed estrogen. *(Lacey et al)* A 2009 Danish study found a 38 percent increased risk of ovarian cancer in all hormone users, *(Greiser et al)* and a 1976 – 2002 arm of the Nurses' Health Study found a 25 percent increase in the risk of ovarian cancer for every five years of using unopposed estrogen. *(Danforth et al)*

Estrogen-only has been found to be beneficial in the prevention of Alzheimer's and dementia in both retrospective and prospective studies, but the credibility of this research is called into question by small sample size. In the WHI, estrogen-only was found to increase the risk of dementia. *(Paganini-Hill, Kawas, Tang, Shumaker)*

Risks Associated with No Ovarian Hormone Production

More than half of women who have a hysterectomy have reduced ovarian function within two years. This is likely because the uterus and ovaries share blood supply. Oophorectomized women are in immediate surgical menopause, and are also deprived of the androgens that the ovaries make long after menopause, which are converted to estrogen in fatty tissue.

Although women whose ovaries are removed, or whose ovaries atrophy after hysterectomy have a lower risk of breast, endometrial and ovarian cancer if they don't use hormone replacement, they do have an increased risk of premature death, cardiovascular disease, cognitive impairment or dementia, parkinsonism, osteoporosis and bone fractures, decline in psychological wellbeing and decline in sexual function. *(Kritz et al, Shuster et al)*

The Benefits of Progesterone

Natural progesterone has a long history of being excluded from hormone replacement and research in the U.S., in favor of the progestins, and yet progesterone and progestins have dramatically different actions and effects. (Reproductive endocrinologists are well aware of the difference, as the progestins cannot be used in fertility treatments.) Further confusion is caused by semantics, in which some researchers considered progestins to be a generic term for all compounds with progesterone-like activity, while others delineate (natural) progesterone from the man-made progestins. In Europe, the term progestogen is used as a generic terms for all progesterone-like compounds, including progesterone.

In the late 1990s, so-called natural progesterone creams began to be used in alternative medicine, and by now have made significant inroads into doctor's offices across the U.S. It is estimated that some 2 million menopausal women in the U.S. are using oral (micronized) or transdermal progesterone. The terms natural progesterone or bioidentical hormones are often used to make the distinction between progesterone and progestins, although these usages are often criticized as being marketing terms rather than scientific terms.

Adequate levels of progesterone are associated with a reduced risk of breast cancer, heart disease, ovarian cancer, endometrial cancer and osteoporosis. Progesterone is used to treat infertility, preterm labor and brain injuries.

In 1945 fertility researchers Cowan et al at John Hopkins University measured endogenous progesterone levels in 1083 women and followed them for 20 years. Those with the highest levels of progesterone at the outset had a significantly lower risk of breast cancer, and those with the lowest levels had the highest risk of breast cancer. Women in the progesterone deficiency group had 5.4 times the risk of premenopausal breast cancer compared to women with normal progesterone levels. Women in the progesterone deficiency group also experienced a 10-fold increase in deaths from all malignant neoplasms compared to the normal hormone group.

In 1995, research was published on a group of 40 women scheduled for breast surgery (cosmetic or cyst removal) who applied a gel containing either estradiol, progesterone, estradiol plus progesterone, or a placebo to their breasts for two weeks before surgery. Tissue samples taken at the time of surgery were used to measure the amount of hormone in breast tissue, as well as cell proliferation rates. Both hormones were well absorbed. Estradiol increased cell proliferation rates by 230 percent, while progesterone decreased proliferation by more than 400 percent. The estradiol/progesterone combination maintained a normal proliferation rate. (Chang et al)

Micronized progesterone has been widely used in Europe since the early 1980s, particularly in France, where the ongoing E3N Cohort followed nearly 100,000 women for more than a decade. This has provided an opportunity to study the HRT combination of estradiol and oral (micronized) progesterone. In 2008, with eight years of follow-up, data was released from E3N showing that women using HRT consisting of estradiol and a progestin had a 69% higher risk of breast cancer, while women using estradiol plus progesterone had the same risk as women using no HRT. *(Fournier et al)*

A 2010 release of information from the E3N, published in JAMA, examined the risk of stroke among women using oral (pill) estrogen, transdermal estrogen (patch or gel), different kinds of progestins, and progesterone. Estrogen patches and gels were shown to be safer than estrogen pills, and progesterone was safer than any of the progestins. In fact, women using estrogen patches and oral progesterone had a slightly lower risk of stroke compared to women not using any type of hormone replacement. *(Fournier et al)*

The major studies that are brought forth to prove that HRT does not improve cardiovascular function including the WHI, HERS and others should not be taken as proof

that HRT does not improve cardiovascular function. These studies have all used estrogen plus a progestin. Multiple studies have highlighted the cardiovascular differences between progesterone and progestins. One of these was the Postmenopausal Estrogen/Progestin Intervention (PEPI) trial that showed that women who received micronized progesterone had significantly increased HDL levels over women who received MPA. Multiple studies have shown that progestins blunt the positive effects of estrogen. This is not the case with progesterone. In a 2000 study, researchers studied women with stable angina and prescribed either estrogen plus MPA or estrogen plus transvaginal progesterone. Exercise time to myocardial ischemia was significantly increased with progesterone vs. estrogen plus MPA or even vs. estrogen alone *(Rosano, et al.)* Finally, unopposed estrogens, particularly oral estrogens increase the risk of venous thromboemobolism. In a 2007 study of data from the ESTHER trial published in Circulation, showed that estrogen plus progesterone yielded the same low risk of VTE as transdermal estrogen alone *(Canonico, et al.)*

During the past decade, many discoveries have been made about progesterone's effect on the nervous system. In particular, it promotes the viability of neurons in the brain and spinal cord, being an essential component of the myelin sheath that protects nerves. It is currently used in emergency rooms across the U.S. to treat victims of traumatic brain injury, and is showing promise in treating ischemic stroke and improving brain function in the elderly. According to Emory University researchers, "...[progesterone] may promote neuroregeneration by several different actions by reducing inflammation, swelling and apoptosis, thereby increasing the survival of neurons, and by promoting the formation of new myelin sheaths. Recognition of the important pleiotropic effects of progesterone opens novel perspectives for the treatment of brain lesions and diseases of the nervous system." *(Schumacher, Stein)*
New information about progesterone in the brain shows that progesterone increases brain derived neurotrophic factor (BDNF). Progesterone is metabolized to allopregnenolone which is a major protective metabolite and plays a role in the neuroprotective effects of progesterone. Progestins on the other hand have been shown to have the opposite effect in the brain. Medroxyprogesterone acetate (MPA) inhibits BDNF which may have adverse consequences in the brain. MPA does not convert to allopregnenolone, the metabolite that is thought to be neuroprotective *(Singh and Su)*.

A 2008 literature review of HRT in the journal Maturitas concluded "...a growing literature suggests that the progestins used in association with estrogens may not be equivalent. Recent evidence indeed shows that natural progesterone displays a favorable action on the vessels and on the brain, while this might not be true for some synthetic progestins. Compelling indications also exist that differences might also be present for the risk of developing breast cancer, with recent trials indicating that the association of natural progesterone with estrogens confers less or even no risk of breast cancer as opposed to the use of other synthetic progestins. In conclusion, while all types of hormone replacement therapies are safe and effective and confer significant benefits in the long-term when initiated in young postmenopausal women, in specific clinical settings the choice of the transdermal route of administration of estrogens and the use of natural progesterone might offer significant benefits and added safety." *(L'Hermite et al)*

In women whose hormone production is compromised or absent due to removal of the uterus and/or ovaries, it is beneficial to replace progesterone along with estrogen, for the health of the cardiovascular system, breasts, brain and nervous system.

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