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REPORT

Estriol: Its Weakness is Its Strength

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Estriol, an estrogen that has virtually been ignored by the mainstream medical community, is one of the three principal estrogens produced by the body. Estriol was originally thought to have little significance due to its weak estrogenic activity when compared with estrone and estradiol. Nonetheless, research has found that its weakness may very well be its strength.

Studies suggest that when the lower-potency estrogen, estriol, is administered topically, it does not increase the risk of hormone-dependent cancers of the breast or endometrium (uterine lining).[1-3] However, having weaker estrogenic effects does not mean that estriol has none of the benefits that come with more potent estrogens. Studies suggest that estriol reduces symptoms of menopause, such as hot flashes and vaginal dryness, but with a better safety profile compared with more potent estrogens.[1,4,5] This makes estriol a better choice for bioidentical hormone-replacement treatment regimes.

That is not all this 'weak' hormone is good for! Research suggests that estriol has benefits for bone density, heart health, multiple sclerosis, and postmenopausal urinary tract health.[6-12] In this article, we will review the attributes of this 'weaker' estrogen, and why this estrogen is currently in the news.

WHAT YOU NEED TO KNOW: ESTRIOL

- The body naturally makes three estrogen hormones—estradiol, estrone, and estriol. Since estriol possesses the weakest estrogenic effects of the three, it has been largely overlooked by the medical community.
- Many studies show that estriol offers a wealth of potential health benefits—without the dangers that sometimes accompany higher-potency estrogens and synthetic or horse-derived hormones.
- Studies suggest that estriol helps relieve menopausal symptoms while benefitting bone and urinary tract health. Estriol may also help improve cardiovascular risk factors and even shows promise in reducing the brain lesions of multiple sclerosis.
- The most reliable way to measure estriol levels is through 24-hour urine collection.
- Despite abundant evidence to the contrary, the FDA has recently claimed that estriol is not safe. You can act now to help preserve consumers' access to bioidentical hormones such as estriol by visiting www.homecoalition.org.
- Fear of cancer prevents many women from restoring youthful hormone levels. When applied through the topical (transdermal) route, estriol is not associated with increased cancer risk. Other methods women can use to prevent hormone-related cancers include consuming abundant vitamin D, cruciferous vegetables, soy, D-glucarate, and lignans, while minimizing meat and high-fat dairy intake.

ESTRIOL AND HORMONE REPLACEMENT THERAPY

If you are on hormone-replacement therapy (HRT) and have never heard of estriol, you might be wondering why not? Before the 1970s, estriol was thought to have significance only during pregnancy. Levels of estriol are elevated in pregnancy up to 1,000 times compared with normal non-pregnant levels.

In the 1960s, we saw the beginning of hormone-replacement therapy with patented equine estrogens such as Premarin® and synthetic progestins as found in Provera®. By the 1990s, one-third of menopausal women were taking Premarin®. Research uncovered the increased incidence of breast cancer, increased risk of blood clotting, and increased cardiovascular risk associated with the use of these horse-derived and synthetic hormones (used in combination in the patented medication Prempro®).[13] The medical community began to wonder if using hormones from pregnant horses was such a good idea. In an effort to find a safer alternative, many patients and practitioners began looking into 'natural' hormone-replacement treatment using bioidentical hormones, which are identical to those produced naturally within the body. Bioidentical-hormone replacement was pioneered in the 1980s as a treatment for menopause by Dr. Jonathan Wright in Washington state.

Interest in estriol increased as it was discovered that estriol was safer than horse-derived and synthetic hormones in relation to cardiovascular health and potentially cancer risk. Unfortunately, many doctors have not adopted its use, and many bioidentical hormone-replacement regimes use only estradiol, a more potent estrogen with increased associated risks.

The benefits of estriol may, in part, be explained by the mixed pro-estrogenic and anti-estrogenic effects of this interesting estrogen hormone. Scientists Melamed et al. investigated the mixture of stimulating and non-stimulating effects posed by estriol upon estrogen receptors. When estriol is given together with estradiol, the estradiol-specific stimulation to cells is decreased. This little-appreciated scientific fact helps to explain how estriol can reduce pro-carcinogenic effects of more powerful estrogens like estradiol. However, when estriol is given alone over a long period of time, it can produce a more complete pro-estrogenic effect, explaining why symptom relief is achieved when menopausal women take estriol.[2] Experimental studies suggest that both estriol and tamoxifen (a synthetic anti-estrogen) have protective effects against radiation-induced cancer of the breast.[14]

SAFETY CONCERNS

Most of the research cited in this article used oral estrogen as the route of administration. However, for enhanced safety, topical estriol would be a better choice. Several studies have shown that transdermal estrogen confers less health risk as a route of administration than oral estrogen.[3,21-25] Clinical experience of many doctors over the past 20-30 years suggests that transdermal estrogen is also more effective for some women. This is largely thought to be due to the 'first-pass effect'—meaning that orally ingested drugs are often first metabolized in the liver, before having any activity in the body. Orally ingested estrogen hormones are among these drugs that are first metabolized in the liver before exerting their effects in the body. Physicians experienced in hormone replacement often observe that women treated with oral estrogens show high levels of estrogen metabolites in 24-hour urine specimens, suggesting that most of the orally ingested hormones are being excreted.

In addition, several studies suggest that bioidentical estrogen has less health risk when given with low doses of bioidentical progesterone.[26,27]

In a prospective study funded by the US Army and performed at the Public Health Institute, Berkeley, California, researchers compared estriol levels during pregnancy with breast cancer incidence 40 years later. Results revealed that of the 15,000 women entered in the study, those with the highest levels of estriol relative to other estrogens during pregnancy had the lowest cancer risk. In other words, as the relative level of estriol increased during pregnancy, risk of breast cancer decreased 40 years later. In fact, women with the highest level of estriol during pregnancy had 58% lower risk for breast cancer compared with women who had the lowest serum estriol levels. The authors also noted that Asian and Hispanic women had higher estriol levels compared with other racial groups. Interestingly, Asian and Hispanic women have the lowest breast cancer rates. The authors concluded, "If confirmed, these results could lead to breast cancer prevention or treatment regimens that seek to block estradiol estrogen action using estriol, similar to treatment based on the synthetic anti-estrogen tamoxifen."[15]

In another study, Takahashi et al. studied the safety of estriol treatment for menopausal symptoms. Fifty-three women with either surgically induced or natural menopause were given 2 mg of oral estriol/day for 12 months. Endometrial and breast assessments done with endometrial biopsy and breast ultrasound, respectively, found normal results in all women. The authors concluded that over a 12-month period, "estriol appeared to be safe and effective in relieving symptoms of menopausal women."[1]

In one investigation, 52 postmenopausal women were given 2 mg, 4 mg, 6 mg, or 8 mg/day of oral estriol for six months. In all patients, vasomotor symptoms of menopause (such as hot flashes) were decreased. The most improvement was experienced by women taking the highest dose of 8 mg. There were no signs of endometrial hyperplasia confirmed by endometrial biopsy over the six-month treatment period. Mammograms were obtained on six of the patients who had mammary hyperplasia at the study's outset, and no further changes were seen.[8]

Although the oral route of administration of estriol appears relatively safe over the short-term, the transdermal route is preferred for

long-term use. For example, Weiderpass et al. found an increased risk of endometrial atypical hyperplasia and endometrial cancer with oral use of estriol, but not with transdermal estriol over at least a five-year period. Compared with no use of estriol, those who took oral estriol for at least five years had a significantly greater risk, compared with individuals who did not take any estriol. Women using topical estriol for at least five years did not have any increased risk.[3] As you will read in the “Safety” box, several studies suggest that the use of topical natural progesterone cream may further reduce the risk to the endometrium.[16-18]

Henry Lemon, MD, a women’s cancer specialist, took this research one step further and developed the concept of the estrogen quotient—the ratio of estriol to the sum of estradiol and estrone (estriol/estrone+estradiol). By looking at this ratio of ‘good’ estrogen to ‘bad’ estrogen, a physician can evaluate breast cancer risk and prescribe estrogen replacement better tailored to the individual to reduce cancer risk. The estrogen quotient can be evaluated from a 24-hour urine hormone panel.[19,20]

ESTRIOL REDUCES MARKERS OF CARDIOVASCULAR RISK

Growing evidence suggests that estriol may offer protective benefits for the cardiovascular system. For instance, Takahashi et al. found that some women with natural menopause given 2 mg/day oral estriol for 12 months had a significant decrease in both systolic and diastolic blood pressure.[1]

Another study compared the use of oral estriol at a dose of 2 mg/day for 10 months in 20 postmenopausal and 29 elderly women. Some of the elderly women had decreases in total cholesterol and triglycerides and an increase in beneficial high-density lipoprotein (HDL).[7]

ESTRIOL IMPROVES BONE MINERAL STATUS IN WOMEN WITH OSTEOPOROSIS

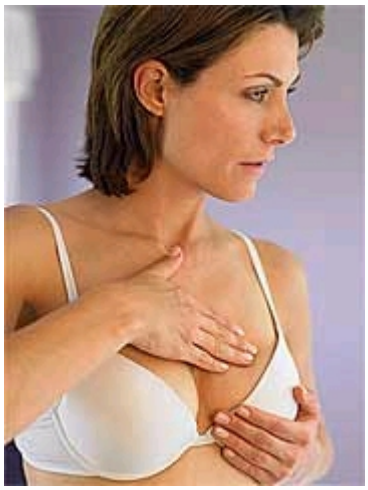
A Japanese study involving 75 postmenopausal women found that after 50 weeks of treatment with 2 mg/day of oral estriol cyclically and 800 mg/day of calcium lactate, women had an increase in bone mineral density, a decrease in menopausal symptoms, and no increased risk of endometrial hyperplasia (tissue overgrowth that may precede cancer).[6]

Similarly, Nishibe et al. investigated treatment of postmenopausal and elderly women with 2 mg/day of oral estriol and 1,000 mg/day of calcium lactate versus 1,000 mg/day calcium lactate alone. The bone mineral density significantly increased in women who received estriol, whereas the women who did not take estriol experienced a decrease in bone mineral density.[7]

ESTRIOL REDUCES BRAIN LESIONS OF MULTIPLE SCLEROSIS

The high levels of estriol during pregnancy have been known to alleviate some autoimmune conditions due to its ability to shift immune response.[9] For instance, Sicotte et al. at the Reed Neurological Research Center in Los Angeles investigated the effects of pregnancy-level doses of estriol (8 mg/day) in non-pregnant women with multiple sclerosis (MS). Cerebral MRI images showed a significant reduction of gadolinium-enhancing cerebral lesions from multiple sclerosis. These lesions increased when treatment stopped and decreased when treatment was restarted.[28] Gadolinium is a contrast agent used in certain MRI studies; gadolinium-enhancing lesions are associated with an increased inflammatory response marking disease progression in patients with MS. Lowered amount of these lesions seen on MRI with gadolinium contrast would equate to a decrease in disease progression.

This effect may also apply to men with autoimmune conditions. Another team of researchers from the Reed Neurological Research Center in Los Angeles found that estriol treatment ameliorates experimental autoimmune encephalomyelitis (EAE) in males, compared with placebo treatment.[29] EAE is an experimental demyelinating inflammatory disease that shares numerous characteristics with MS. Estriol treatment also resulted in a decrease of proinflammatory immune markers. This is very promising news for patients and their doctors who are struggling to treat challenging neurological conditions associated with inflammation.



ESTRIOL PROTECTS URINARY HEALTH IN POSTMENOPAUSAL WOMEN

Postmenopausal women who suffer from incontinence or recurrent urinary tract infections will be pleased to know that estriol offers benefit in the context of these troublesome conditions. In a prospective, randomized, placebo-controlled study, 88 women were given 2 mg intravaginal estriol suppositories (once daily for two weeks, then twice weekly for six months) or placebo. Of the women in the estriol group, 68% reported improvement in symptoms of incontinence. In addition, measurements of mean maximal urethral pressure and mean urethral closure pressure were significantly improved.[10]

In another randomized, double-blind, placebo-controlled trial, women with recurrent urinary tract infections (UTI) were given either intravaginal estriol cream (containing 0.5 mg estriol, once daily for two weeks, then twice weekly for eight months) or placebo.

The incidence of urinary tract infection was dramatically reduced in the estriol group compared with placebo (0.5 versus 5.9 episodes per year).[11]

MEASUREMENT OF ESTRIOL

Hormones produced by the body are secreted in pulses, while hormones taken transdermally or orally will initially be very high and slowly decline over the course of the day. This scientific reality makes testing for estriol at a single point in time—as would be the case for saliva or serum testing—very inaccurate. There are too many variables: When did your body last put out a pulse of the hormone under investigation? When did you take your hormone-replacement therapy? Estriol in particular does not last very long in the blood. In fact, the half-life of estriol has been shown to be between 3.6 and 64 minutes.[30]

The more accurate way to assess estriol is by collecting what is excreted during a 24-hour urine collection. This form of testing ensures that we have an accurate value that is not affected by the fluctuations of the day, because we are measuring 24 hours' worth of hormone production.

ESTRIOL IN THE NEWS

Recently, the FDA made claims that estriol—a hormone naturally produced by women's bodies—is not safe, even though the FDA did admit at a press conference that no adverse effects from estriol have ever been reported. After reading about the benefits of estriol that research has uncovered, it is hard to understand why the FDA would want to take this more protective estrogen off the market and out of reach of the many thousands of women seeking relief from menopausal and postmenopausal symptoms.

This recent attack on estriol also includes all bioidentical hormones produced by compounding pharmacies. Why are these substances such a threat? This is not the first time the FDA has made attacks on unpatented natural substances. Bioidentical and therefore unpatentable hormones are a threat to the income of big drug companies. The fees paid by these big drug companies are a large portion of FDA income. Would you not say that there is a conflict of interest here? Why would any woman want to take horse estrogen or chemically imprecise, yet patentable estrogen rather than estrogen that is identical to that produced by women's own bodies? This is even more questionable in the light of all the negative research showing increased health risks from these FDA-approved substances. And is it not the job of the FDA to make sure that women get safe and effective medicine? It seems the FDA has largely lost sight of its original goals. For more information on this and to take action, please visit the HOME (Hands Off My Estrogen!) Coalition website at www.homecoalition.org.

SUMMARY

Estriol, once thought of as insignificant and weak, actually has protective effects against stronger estrogens. For this reason, it is a relatively safer choice for bioidentical hormone-replacement therapy. We have learned that safety is also increased by using topical administration instead of oral administration, and by balancing estrogen with progesterone. Estriol has benefits beyond treating typical postmenopausal symptoms. Estriol offers potential benefit for people with MS, postmenopausal women prone to urinary tract infection or incontinence, and menopausal/ postmenopausal women with osteoporosis. It would be a great shame to lose this wonderful tool before it was ever fully utilized.

If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

IS FEAR OF CANCER A REASON TO BE DEPRIVED OF HORMONES?

As women enter their menopausal years, they face a difficult decision. The body's natural production of estrogen, progesterone, dehydroepiandrosterone, and other critical hormones needed to maintain health and vigor rapidly declines.[31,32] While individual effects of menopause vary widely, most women suffer because their glands no longer produce the hormones needed to regulate critical physiological processes. Depression, irritability, and short-term memory lapses are common menopausal complaints, along with hot flashes, night sweats, and insomnia.[31]

Concern about cancer is the primary reason why women do not restore their hormones to more youthful levels. Like much of what we eat, estrogen and testosterone affect cell proliferation. Does that mean we should shrivel up, degenerate, and die from these sex hormone deficiencies we all face as a part of "normal" aging?

Based on the data showing how people may reduce their rate of cancer and favorably affect estrogen metabolism in a way that points to cancer prevention (by consuming lots of cruciferous vegetables, for example), it is difficult to buy into the argument that natural sex hormones should only be enjoyed by the young.

Large human population studies show huge reductions in cancer risk and specific protective mechanisms against estrogen's negative pathways when vitamin D,[32-36] cruciferous vegetables (a source of indole-3-carbinol, or I3C),[37-42] soy,[43-48] D-glucarate,[49-52] and lignans[53-55] are consumed. Dramatic cancer rate reductions also occur when red meat, high-fat dairy, and other deleterious foods are reduced or eliminated from the diet.[43,55-58]

Misconceptions generated by conflicting studies and media hype have created an environment in which aging people suffer the agonies and shortened life spans caused by sex hormone imbalances, yet do nothing to correct this due to fear of cancer. When one looks at what the real cancer risk factors are, it would appear that altering one's lifestyle at any age would result in significant reductions in malignant disease, including those who properly restore their natural hormone balance to reflect a more youthful range.

THE REAL CAUSE OF BREAST CANCER

To enable members to fully understand the carcinogenic effects of aging, we have reprinted on this page a chart showing women's breast cancer risk by age.[59] A quick look at this chart clearly documents that aging is the primary cause of breast cancer. The good news is that the gene expression changes involved in the development of breast cancer can be favorably altered by taking low-cost nutrients like vitamin D60 in the dose of 1,000 IU to 10,000 IU/day, based on individual need.

RISK OF DEVELOPING BREAST CANCER BY AGE[59]

By age 25: 1 in 19,608
By age 30: 1 in 2,525
By age 40: 1 in 217
By age 45: 1 in 93
By age 50: 1 in 50
By age 55: 1 in 33
By age 60: 1 in 24
By age 65: 1 in 17
By age 70: 1 in 14
By age 75: 1 in 11
By age 80: 1 in 10
By age 85: 1 in 9

During the younger years, when breast cancer is virtually non-existent, we enjoy high levels of our sex hormones (estrogen, progesterone, dehydroepiandrosterone, and testosterone). As we age and hormone levels decline, breast cancer risks increase. The reason "aging" causes cancer is that the genes in our cells that regulate cell proliferation become increasingly mutated. The accumulation of mutations to our cells' regulatory genes is the underlying cause of cancer.[61] It is encouraging to know that there are low-cost nutrients that favorably restore healthy gene function and reduce our risk of cancer in the process.

A newly published study cites evidence that vitamin D can exert its cancer-preventing effect by counteracting the growth-promoting effect of estrogens.[62] Vitamin D also exerts its cancer-preventive influence by helping to control cell differentiation and inducing normal programmed cell disposal (apoptosis).[62]

Based on the enormity of these data, it would appear that aging humans can restore many of the hormones they need to sustain life—without encountering adverse effects. Having said this, we have to remind readers that there are still no long-term safety data on the safety of even weak exogenously administered estrogens like estriol. Based on the totality of evidence that exists to date, it would appear that the estriol confers many benefits, while definitive protective measures against breast and other cancers can easily be incorporated into a healthy lifestyle.

—William Faloon

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