

Examining the safe and effective use of estrogen replacement for menopausal women

Abstract

There are a number of estrogen hormones that decline during menopause, causing various symptoms and conditions. Estrogen replacement therapy (ERT) is a common medical therapy to treat these symptoms and conditions. The safe use of ERT has a controversial past, but more recent studies demonstrate that when appropriately prescribed, ERT can be used safely and with good efficacy. As well, there has been a better understanding in recent years of the definition and use of bioidentical estrogen.

Keywords: estrogen replacement therapy, ERT, menopause, bioidentical, bioidentical estrogen, bioidentical HRT, progesterone, Women's Health Initiative

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Introduction

Estrogens are a group of steroidal hormones that have numerous physiological effects on women. The decline in estrogen levels during the menopausal and postmenopausal years is associated with several signs, symptoms, and health risks. Extensive research has demonstrated that appropriate prescription of estrogen replacement therapy can safely and effectively prevent and treat some estrogen deficiency-related symptoms and diseases. This paper will examine the literature on the safe and effective use of estrogen replacement during the menopausal transition.

Overview of estrogen

The term estrogen refers to a group of related steroidal hormones. There are three primary estrogens produced by females, which are estrone (E1), β -estradiol (E2), and estriol (E3).¹ The levels and activity of these hormones change from premenopause through postmenopause. β -estradiol is the most biologically active estrogen with approximately 12 times the potency of estrone and 80 times that of estriol.¹

Melmed and coauthors summarize the premenopausal status synthesis and secretion of estrogen as follows:² The central and most biologically active hormone secreted by the ovaries is estradiol. It can however also be produced in many other tissues, such as adipose tissue, brain, bone tissues, vascular endothelium, and aortic smooth muscle cells.³ Estrone is also mainly produced by the ovaries, as well as in the peripheral tissues, by conversion of androstenedione. Finally, estriol is produced in the peripheral tissues by the conversion of estradiol and estrone.

Indications for estrogen replacement

A study investigating the prevalence and severity of menopausal symptoms in older postmenopausal women concluded that there is a high prevalence of moderate to severe vasomotor symptoms in women aged 60 to 65 years.⁴ Menopausal estrogen deficiency has also been demonstrated to accelerate aging.⁵ The decreasing levels of estrogen during the menopausal transition are associated with cardiovascular disease, osteoporosis, urogenital atrophy, skin aging, increased risk of colon cancer, more malignant breast cancer forms, loss of neurons from the brain that results in cognitive decline and earlier expression of Alzheimer's disease, macular degeneration, and cataract formation.⁵ Estrogen replacement therapy (ERT) is an accepted therapy for

postmenopausal women for the treatment of among others vasomotor symptoms, prevention of bone loss, reduction of fracture risk, and reduction of genitourinary symptoms such as vulvovaginal atrophy.⁶

In addition to being a treatment of menopausal symptoms, ERT is also FDA-approved for the treatment of premature hypoestrogenism.⁶ This approval is vital since recent research has demonstrated significantly higher risks of premature menopause (i.e., ovarian failure before age 40) for premature death, neurological diseases, psychosexual dysfunction, mood disorders, osteoporosis, ischemic heart disease, and infertility.⁷ Thus, ERT for premature hypoestrogenism is considered standard of care.⁷ Moreover, there is also research showing that the avoidance of ERT in women aged 50 to 59 years who had a hysterectomy resulted in an excess of these women dying prematurely.⁸ It was estimated that over ten years 91,610 postmenopausal women had died prematurely due to avoiding estrogen therapy.⁸

There are several positive benefits of ERT that go beyond vasomotor symptoms that clinicians should be aware of for menopausal and postmenopausal symptoms.

The Safe and effective use of ERT

Many physicians have been hesitant to prescribe ERT due to the initial release of results from the 2002 Women's Health Initiative (WHI). This trial linked hormone replacement therapy (HRT) to increased breast cancer, cardiovascular disease, and stroke.⁹ The WHI trial included two groups of women between the ages of 50 to 79 who received either oral conjugated equine estrogens (CEE) plus oral medroxyprogesterone acetate (MPA), or oral CEE alone. Later reviews of the WHI study have however concluded that the initial results reported were "misleading and distorted for publicity".¹⁰ One of the criticisms of the study was that the average age of the women in the study was 63 when women are more susceptible to heart disease and breast cancer and that this age is not reflective of the age when women enter menopause.⁹

There is now general agreement, after re-analysis of the WHI data, that there is no increased risk of breast cancer for women under age 60 who take HRT for less than 5.6 years.¹⁰ In addition, there is the benefit of reduced heart disease risk for women closer to menopause.¹⁰ Even the conservative North American Menopause Society summarizes the lack of a correlation between breast cancer risk and estrogen replacement by stating:

Compared with women who received placebo, women who received CEE [synthetic estrogen] alone in the WHI showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with 7 fewer cases of invasive breast cancer per 10,000 person-years of CEE [synthetic estrogen]. The nonsignificant pattern of reduction in breast cancer remained evident for up to a median 13 years cumulative follow-up.... Limited observational evidence suggests that HT [hormone therapy] does not further increase risk of breast cancer in women with a family history of breast cancer or in women after oophorectomy for BRCA1 or 2 gene mutation.⁶

The use of progestogen is recommended for women supplementing ERT to prevent endometrial hyperplasia or cancer.⁶ However, progestins, the synthetic forms of progestogen,¹¹ have been shown to increase the risk of breast cancer¹² by inducing abnormal cell proliferation.¹³ There is also research demonstrating that estrogen plus progestin increases mortality in postmenopausal women.¹⁴ The bioidentical form of progestogen, known as progesterone, is available in oral and transdermal form. Some observational studies suggest that breast cancer risk is lower with bioidentical micronized progesterone in oral form.⁶

As noted earlier, the appropriate use of ERT has many potential benefits for women. There are many routes of administration for ERT. These include oral as well as transdermal forms (patches, sprays, gels, creams, injections, and pellets), while for vaginal use also suppositories, creams, and rings are available. There appear to be safety advantages with the non-oral forms as they bypass the first hepatic effect.⁶ For example, transdermal ERT reduces the formation of clotting factors and other proteins associated with the oral form that induce the first hepatic effect.¹⁵ The transdermal form also offers a reduced risk of deep vein thrombosis and pulmonary thromboembolism compared to oral estrogens, as well as advantages for blood pressure control.¹⁵ Additionally, oral ERT is converted into estrone more readily, which does not have the symptom-relieving effect of estradiol, thus rendering the therapy less effective.¹⁶ Moreover, other benefits of the transdermal form may include better stability of blood estradiol levels, reduction of LDL cholesterol and total cholesterol while not elevating triglycerides (as can occur with oral estrogen), and unlike oral estrogen, it does not increase the production of the inflammation biomarker C-reactive protein by the liver.¹⁶

Potential side effects of ERT

The main potential side effects of estrogen include bloating, breast tenderness or swelling, headaches, indigestion, feeling sick, and vaginal bleeding.¹⁷ Also, venous thromboembolism is a known risk with oral ERT but not with transdermal administration.^{15, 18} Oral estrogen increases the risk of cholelithiasis, cholecystitis, and cholecystectomy.⁶ Unopposed systemic ERT increases the risk of endometrial cancer in postmenopausal women with an intact uterus.⁶ Whether ERT is a risk factor for breast cancer after long term use is still unclear.⁶ ERT is not generally advised for breast cancer survivors, however, low-dose vaginal ERT is an option for women with genitourinary syndrome of menopause.⁶

The benefit of bioidentical ERT

Historically, in the United States, CEE, also known as Premarin, has been the most commonly prescribed form of ERT. In the last two decades, the use of bioidentical ERT has, however, become more

common. The term bioidentical hormones can be defined as molecules that are identical in composition and structure to human hormones.¹⁹

One review evaluated studies comparing bioidentical hormones including estradiol, estriol, and progesterone to non-bioidentical (synthetic and animal-derived) HRT.²⁰ The author of this study concluded that bioidentical hormones were more effective and associated with lower risks of breast cancer and cardiovascular disease than synthetic or animal-derived versions.²⁰ The author did agree with a comment on his article that there is a need for further investigation on the effect of bioidentical hormones on cardiovascular outcomes and that more control trials should be completed comparing bioidentical and non-bioidentical hormones.²¹ Bioidentical estrogen is available in transdermal, oral, patch, and vaginal forms.

Conclusion

In conclusion, the appropriate indications for ERT include women with premature hypoestrogenism, vasomotor symptoms, prevention of bone loss, and genitourinary symptoms. One type of ERT that should be considered by clinicians is bioidentical ERT, especially in a transdermal form. For women with a uterus, ERT should be combined with micronized oral progesterone to prevent endometrial hyperplasia and cancer.

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Conflicts of interest

The author declares there is no conflict of interest.

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