When Lowest Dose for Shortest Amount of Time Does Not Apply

Stephanie S. Faubion, MD,¹ Julia A. Files, MD,² and Walter A. Rocca, MD^{3,4}

Case History

A 42-YEAR-OLD woman gravida 2, para 2 underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy (BSO) 2 years ago (age 40 years) for severe endometriosis involving both ovaries. She was started on estrogen therapy (ET) a few weeks after surgery, but she stopped it after 1 year because she had concerns about being on hormone therapy. She has mild hot flashes and an occasional night sweat. She also reports changes in mood with some irritability and anxiousness. She is experiencing vaginal dryness and insertional dyspareunia, which is not sufficiently relieved with the use of vaginal moisturizers and lubricants. She is using stress management techniques, avoidance of triggers, and regular exercise to help manage her vasomotor symptoms. She seeks your advice regarding management of her symptoms.

Based on current evidence, you advise:

- A. Continue with lifestyle modification because she only has mild vasomotor symptoms.
- B. Prescribe local vaginal ET for vaginal dryness.
- C. Prescribe a selective serotonin reuptake inhibitor for management of her vasomotor symptoms and her mood disturbance.
- D. Answers A, B, and C are all correct.
- E. Prescribe systemic ET to reduce the risk of adverse long-term health consequences.

Discussion

Menopause for most women occurs between the ages of 46 and 55 years, but about 5% of women experience menopause early, between the ages of 40 and 45 years. Approximately 1% of women experience menopause prematurely, before the age of 40 years. BSO is the most common reason for premature or early menopause.¹ Multiple adverse long-term health outcomes are associated with premature or early menopause, including coronary heart disease, dementia, parkinsonism, glaucoma, osteoporosis, mood disorders, sexual dysfunction, and early death. Although replacing estrogen reduces some of these risks, it may not completely eliminate the increased risk of parkinsonism, glaucoma, mood disorders, and sexual dysfunction.²

Reproduction is not the only function of the ovaries. The ovaries are also an endocrine organ with important functions mediated by receptors for ovarian hormones found in most tissues and organs. Premenopausally, the ovaries secrete primarily estrogen, progesterone, and testosterone, whereas postmenopausally, they secrete primarily testosterone, androstenedione, and dehydroepiandrosterone.³ Surgical removal of the ovaries before the natural age of menopause or primary ovarian insufficiency (POI) results in loss of estrogen, progesterone, and testosterone. Irrespective of the cause, women experiencing premature or early menopause are exposed to abnormal hormonal deprivation.

The Women's Health Initiative (WHI) trials were not designed to study premature or early menopause (the youngest age of women was 50 years), and the results do not directly apply to these women. Although current clinical practice guidelines suggest the use of the lowest dose of hormone therapy for the shortest time needed to achieve treatment of symptoms in postmenopausal women, this recommendation does not apply to women experiencing premature or early menopause. In women with POI or BSO before the natural age of menopause, the goal of hormone therapy is not simply to manage symptoms, but also to replace the lost endocrine function of the premenopausal ovaries. The old term "estrogen replacement therapy" is a better term for this important medical practice.⁴ The confusion between "estrogen replacement therapy" and "estrogen therapy" (ET) is dangerous, and has caused mistreatment in many women after the publication of the WHI trial results.

Although data are available regarding the range of estrogen doses and estradiol levels needed to preserve and maintain bone health,^{5–7} similar data are not available regarding estradiol levels (serum or tissue) needed to preserve cardiovascular or brain health. Higher doses of estradiol may be needed to approximate premenopausal levels; however, more precise data are lacking. Estrogen-containing contraceptives (which contain much higher doses of estrogen than postmenopausal hormone therapy) are commonly used in women with POI to provide hormone replacement and contraception. For women with early BSO, higher doses of postmenopausal ET (at least the equivalent of 100 mcg of transdermal estradiol)

¹Women's Health Clinic, Division of General Internal Medicine, Mayo Clinic Rochester, Rochester, Minnesota.

²Division of Women's Health Internal Medicine, Mayo Clinic in Arizona, Scottsdale, Arizona.

³Division of Epidemiology, Department of Health Sciences Research, Department of Neurology, Mayo Clinic Rochester, Rochester, Minnesota.

⁴Department of Neurology, Mayo Clinic Rochester, Rochester, Minnesota.

may be needed to provide an estrogen milieu that is physiological for premenopausal menstruating women. A progestogen is needed in addition to ET to protect the endometrium, if the uterus remains intact. However, most women who undergo BSO also undergo hysterectomy (concurrently or preceding).

Unless a strong contraindication exists (such as a hormone-dependent cancer), women with BSO or POI before the age of 45 years will benefit from ET. Several medical societies recommend that hormone therapy be initiated in women with premature or early menopause and continued at least until the natural age of menopause.² Longer duration therapy can be considered if symptoms dictate.⁸

Women with early BSO not only lose estrogen and progesterone but also lose about 50% of their androgen production.⁹ Early BSO is associated with sexual dysfunction,¹⁰ and testosterone has been associated with improved sexual function in women with oophorectomy.^{11,12} The Endocrine Society endorses treatment of postmenopausal women with properly diagnosed hypoactive sexual desire disorder; however, it does not routinely recommend the use of testosterone after BSO or in women with POI.¹³ Questions regarding safety and efficacy of testosterone therapy in women remain, and no Food and Drug Administration (FDA)-approved testosterone preparations for women are currently available in the United States.

Answer: The Correct Answer is E

Answer A is incorrect because the lack of severe vasomotor symptoms is not a reason to avoid treatment with systemic estrogen in this age range. The results of the WHI trials do not apply to women who experience estrogen deprivation at or before age 45 years. ET (or better “estrogen replacement therapy”) is needed to protect against the multiple adverse long-term health consequences of early estrogen deprivation. Answer B is incorrect. Although local vaginal ET may be needed in addition to systemic ET (if systemic ET is not sufficient to treat vaginal symptoms), it does not provide the systemic ET needed to protect the bone, the brain, and the cardiovascular system. Answer C is incorrect for the same reasons. ET may help alleviate mood symptoms associated with menopause in some women; however, a combination of hormone therapy and an antidepressant may be needed if symptoms are severe.¹⁴ Answer D is incorrect because none of the answers include the prescription of systemic ET, which is the first-line therapy.

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Address correspondence to:

Stephanie S. Faubion, MD

Women's Health Clinic

Division of General Internal Medicine

Mayo Clinic Rochester

200 1st Street SW

Rochester, MN 55905

E-mail: Faubion.Stephanie@mayo.edu