CME CREDIT

ONE MINUTE CONSULT

BRIEF QUESTIONS AND ANSWERS ON CURRENT CLINICAL CONTROVERSIES

Q: In postmenopausal women who have had a subtotal (simple) hysterectomy, how much estrogen is enough, and how do you test for deficiency?

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A: MOST POSTMENOPAUSAL WOMEN who have had a hysterectomy can start with one of the following regimens (TABLE 1):

- Conjugated equine estrogens (Premarin) 0.625 mg by mouth daily
- A transdermal estradiol patch (Alora, Climara, Estraderm, Vivelle) 0.05 mg/24 hours, changed every 3 1/2 days for the Alora, Estraderm, and Vivelle patches or weekly for the Climara patch.
- Micronized estradiol (Estrace; also available generically) 0.5 mg by mouth twice a day.

These are the standard minimum dosages for preventing osteoporosis and are usually enough to treat vasomotor symptoms in women who have not had a premature, surgical menopause (oophorectomy). Additional vaginal estrogen therapy in the form of estrogen creams, the estrogen ring (Estring), or estrogen tablets (Vagifem) inserted into the vagina can be used for any residual, symptomatic urogenital atrophy.

ULTRA-LOW-DOSE ESTROGEN

A new trend in estrogen therapy is to use ultra-low doses: eg, either 0.3 mg of conjugated equine estrogen by mouth daily, 0.5 mg micronized estradiol by mouth daily, or 0.025 mg of transdermal estradiol weekly. Ultra-low-dose estrogen therapy may produce fewer side effects and usually controls vasomotor symptoms and protects bone mass; however, we have less experience with these lower doses.

HOW TO TEST FOR ESTROGEN DEFICIENCY

In general, a woman serves as her own bioassay for signs of estrogen deficiency. If she has classic symptoms of menopause such as hot flashes, dry vagina, dyspareunia, or irritable bladder symptoms, she needs systemic therapy, local estrogen therapy, or both.[1] If menopausal symptoms persist after 1 to 2 months of estrogen therapy at the starting dose, the dosage can be increased to 0.9 mg or 1.25 mg of conjugated equine estrogen by mouth daily, 1 mg of micronized estradiol by mouth twice a day, or a 0.075-mg or 0.10-mg estradiol patch.

The dosage depends on whether symptoms persist

TABLE 1

Estrogen replacement dosages for postmenopausal women who have had a hysterectomy

PREPARATIONS	TYPICAL STARTING DOSAGE	SUBSEQUENT DOSAGES*
Conjugated equine estrogens	0.625 mg by mouth daily	0.9 mg, 1.25 mg by mouth daily
Micronized estradiol	0.5 mg by mouth twice a day	1.0 mg by mouth twice a day
Estradiol patch	0.05 mg/24 hours	0.075 mg/24 hours, 0.10 mg/24 hours

*If symptoms persist after 1 to 2 months of estrogen replacement therapy at the starting dosage

CONSEQUENCES OF ESTROGEN DEFICIENCY

Urogenital atrophy. Urogenital atrophy is virtually inevitable in all postmenopausal women who are not on local or systemic estrogen replacement therapy. However, it may not be symptomatic. In general, urogenital atrophy progresses slowly. The highest concentrations of estrogen receptors in the female body are in the vulva, vagina, urethra, and the trigone of the bladder. Patient symptoms and visual inspection are used to evaluate the status of the urogenital tissue and the adequacy of estrogen therapy.

Osteoporosis and cardiovascular disease. Long-term consequences of estrogen deficiency may include osteoporosis and an increased risk of cardiovascular disease and neurocognitive decline. However, these conditions do not occur in all postmenopausal women, and they are also influenced by factors other than estrogen. When prescribing estrogen replacement therapy to prevent or treat osteoporosis, it is generally recommended to keep the total estradiol level at 50 pg/mL or higher. This can be measured by a blood assay. In addition, one can obtain serial measurements of bone density, which correlates well with fracture risk.

ROUTINE ESTROGEN MEASUREMENT IS NOT USUALLY DONE

Nevertheless, we do not routinely measure total estradiol levels because they do not always indicate how much estrogen a woman needs. For example, estradiol levels vary greatly depending on the time of the last oral estrogen replacement dose. In addition, most assays measure biologically inactive estradiol (ie, bound to sex hormone-binding globulin protein) along with the free (active) form of estradiol.

However, the clinician should consider obtaining a total estradiol level if estrogen is being used only to treat osteoporosis or if vasomotor symptoms persist despite what appears to be an adequate dosage of systemic (oral or transdermal) estrogen.

Estrone sulfate is a better measure of estrogenicity than is the total estradiol level because it is cleared slowly and therefore is not subject to daily variations in concentration. In addition, it does not bind to sex hormone-binding globulin protein.

Estrone sulfate serum concentrations are 20-fold higher than those of estrone or estradiol. There are reference ranges for men, for premenopausal women during various phases of the menstrual cycle, for pregnant women, and, most importantly, for postmenopausal women. A recently developed assay for estrone sulfate[2] is available at a few reference laboratories.

Estrone sulfate is a better marker than total estradiol

REFERENCES

1. **Thacker HL.** Women's hormonal health issues: menopause, hormone replacement therapy, and hormonal contraception. In: Stoller JK, Ahmad M, Longworth DL, editors. The Cleveland Clinic Intensive Review of Internal Medicine, 2nd ed. Baltimore (MD): Lippincott, Williams & Wilkins; 2000:13–27.
2. **Ranadive GN, Mistry JS, Damodaran K, et al.** Rapid convenient radioimmunoassay of estrone sulfate. Clin Chem 1998; 44:244–249.

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CME ANSWERS

Answers to the credit test on page 919 of this issue

1 **C** 2 **B** 3 **B** 4 **C** 5 **B** 6 **D** 7 **A** 8 **B** 9 **A** 10 **E** 11 **E**