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Treatment of Women After Bilateral Salpingo-oophorectomy Performed Prior to Natural Menopause

Andrew M. Kaunitz, MD, NCMP, **Ekta Kapoor, MBBS, NCMP**, **Stephanie Faubion, MD, MBA, NCMP**

University of Florida College of Medicine, Jacksonville (Kaunitz); Mayo Clinic, Rochester, Minnesota (Kapoor); Mayo Clinic, Jacksonville, Florida (Faubion).

A 2015 report based on a single US state database observed that among 3002 women younger than 51 years who had undergone bilateral salpingo-oophorectomy (BSO) from 2013 to 2014, 23% had histologically normal ovaries.[1] Strong evidence favors ovarian conservation in the absence of a clear indication for bilateral oophorectomy such as a genetic variant conferring high risk of ovarian cancer.[2] This Insight reviews adverse health effects of BSO in women prior to the age of natural menopause and details treatment of such women.

Surgical menopause is defined as BSO (with or without con-current hysterectomy) prior to menopause. Compared with women who undergo natural menopause, those with surgical menopause experience a more rapid decline in the levels of estradiol and other ovarian hormones that causes more severe vasomotor symptoms (hot flashes, night sweats) and higher rates of mood disorders, sleep disturbances, sexual dysfunction, arthralgias, and reduced quality of life.[2]

Early estrogen deprivation related to premenopausal BSO is associated with an increased risk of a number of long-term adverse health outcomes. Although data from large clinical trials are not available, observational data have shown that while BSO before menopause is associated with a lower incidence of and mortality from breast and ovarian cancers, it is also linked with higher rates of all-cause mortality, coronary heart disease, parkinsonism, cognitive decline, osteoporosis, and accelerated accumulation of multimorbidity defined by 18 chronic conditions associated with aging, including cardiovascular, metabolic, and mental health conditions as well as arthritis and osteoporosis.[3,4] These observational studies have found that some, but not all, potential adverse long-term health outcomes associated with early estrogen deprivation are mitigated by the use of menopausal hormone therapy (MHT; estrogen alone in women who have undergone hysterectomy or estrogen with progestogen in women with an intact uterus).[3,4] To date, no randomized clinical trials have been conducted assessing the effect of MHT (including comparisons of dose, formulation, or route of administration) on disease outcomes including cardiovascular disease, fractures, breast cancer, or dementia in women undergoing BSO before menopause. Therefore, the clinical recommendations regarding MHT offered in this Insight are based on findings from

Corresponding Author: Andrew M. Kaunitz, MD, NCMP, University of Florida College of Medicine, Jacksonville, 653-1 W 8th St, Jacksonville, FL 32209 (andrew.kaunitz@jax.ufl.edu).

observational studies and expert opinion, including guidance from the North American Menopause Society.[5]

General Assessment

Because of the increased risk of cardiometabolic morbidity associated with early estrogen deprivation, including adverse lipid changes, insulin resistance, and increased central adiposity, it is recommended to assess body mass index, blood pressure, hemoglobin A_{1C} level, and a lipid profile in women who undergo BSO before natural menopause.

Maintaining a Healthy Lifestyle

As with other women, clinicians should advise those with early menopause to follow established clinical guidelines for maintaining a healthy lifestyle, including avoidance of tobacco use, moderation of alcohol use, regular aerobic exercise, and a healthy diet to include recommended calcium intake for a postmenopausal woman.

Menopausal Hormone Therapy

Although clinical trials of MHT vs placebo have not been performed in these settings, observational evidence suggests that by replacing the hormones the ovaries would have continued to produce, MHT lowers the risk of long-term morbidities associated with premature (age <40 y) or early (age <45 y) menopause.[3,4] The North American Menopause Society recommends that in the absence of contraindications, MHT should be prescribed for women with surgical menopause before age 45 even in the absence of typical menopause-related symptoms such as hot flashes, night sweats, and sleep and mood disturbances. In this setting, MHT should be continued at least until age 52 years, the average age of menopause (level II evidence).[5]

High-quality data that address the optimal MHT dose or regimen for symptom management, quality of life, or mitigation of potential adverse long-term cardiovascular or skeletal health effects in women with premature or early menopause are lacking. The eFigure in the Supplement details a suggested strategy for initiating and continuing MHT in surgically menopausal women. The Table details selected standard-dose formulations as well as higher doses sometimes needed for symptom management in women with premenopausal BSO. Although data from randomized trials are not available, transdermal estrogen has potentially less risk of venous thromboembolism compared with oral administration,[5,6] and does not increase levels of triglycerides. Accordingly, the transdermal route of administration is preferred for obese women as well as those with metabolic syndrome or diabetes (eFigure in the Supplement). Although estradiol patches, which are available in a wide range of doses, represent the most commonly used form of transdermal estradiol by US women, gels and a spray are also available.[7] Clinicians should take patient preference into account in decision-making about the MHT regimen used. Because premenopausal women commonly use combined oral contraceptives (COCs; numerous formulations are available), some younger menopausal women may prefer to use a COC rather than a regimen designed for menopausal women. However, COCs containing ethinyl estradiol generally use higher

doses of estrogen than those in standard-dose MHT regimens containing 17β-estradiol and appear to have less favorable effects on bone turnover markers.[2,5] MHT formulations may be more effective in preventing osteoporosis than COCs, and there are a variety of combination oral MHT formulations containing estradiol that could be considered. If women do not achieve adequate relief of vaginal dryness and dyspareunia with systemic MHT regimens alone, adding low-dose vaginal estrogen (cream, tablet, insert, or ring) or vaginal prasterone/dehydroepiandrosterone can be considered.[8]

Surgically menopausal women with a uterus should also receive a progestogen along with estrogen to prevent endometrial neoplasia (Table and eFigure in the Supplement). In contrast with medroxyprogesterone acetate, it is unclear whether micronized progesterone in lower doses is sufficient for endometrial protection, particularly when combined with the higher doses of estrogen described in the Table.[9]

In surgically menopausal women older than 52 years, decisions regarding duration of systemic MHT use should be reached through shared decision-making and should take into account potential risks and benefits of MHT as well as treatment goals.[5,10]

BSO before menopause is associated not only with an adverse effect on quality of life, but also with important cardiovascular, neurologic, and skeletal morbidity and mortality. When caring for women with early surgical menopause, clinicians should provide recommendations to minimize the risk of cardiovascular disease and osteoporosis. In addition, they should recognize that in addition to effectively treating menopausal symptoms, MHT may mitigate the potential long-term adverse effects of early estrogen deprivation on bone mineral density, cognitive health, and cardiovascular health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest Disclosures:

Dr Kaunitz reported receiving personal fees from Pfizer and Mithra and research funding to the University of Florida from Mithra outside the submitted work, as well as royalties from UpToDate. Dr Kapoor reported receiving grants from the National Institute on Aging (NIA) (grant U54 AG 44170) during the conduct of the study and serving as a principal investigator for Mithra Pharmaceuticals and receiving personal fees from Astellas Pharmaceuticals outside the submitted work. Dr Faubion reported receiving personal fees from AMAG and Mithra Pharmaceuticals outside the submitted work.

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Table.

Standard and High Doses of Selected Systemic Menopausal Hormone Therapy Formulations[a]

	Standard doses	Higher doses that can be used if symptom control with standard doses is inadequate
Estrogens		
Oral micronized 17β-estradiol	0.5 and 1 mg/d	2 mg/d
Oral conjugated estrogen	0.625 mg/d	0.9 and 1.25 mg/d
Transdermal 17β-estradiol patch[b]	0.0375 and 0.05 mg/d	0.075 and 0.1 mg/d
Vaginal ring 17β-estradiol	0.05 mg/d	0.1 mg/d
Progestogens [c]		
Oral micronized progesterone	100 and 200 mg[d]	≥200 mg[e]
Oral medroxyprogesterone acetate	2.5 and 5 mg[f]	10 and 20 mg (1–2 tablets/d)[g]
Intrauterine levonorgestrel	Levonorgestrel intrauterine system (intrauterine device)	52-mg Device sufficient for higher estrogen doses

Abbreviation: MHT, menopausal hormone therapy.

[a]This table, based on expert opinion, does not detail all available MHT regimens or doses and does not include oral contraceptives.

[b]Transdermal estradiol also available as gels and a spray.[7]

[c]Data are lacking regarding minimum dose of progestogen required for endometrial protection with higher estrogen doses.

[d]Continuous combined regimen with 100 mg daily or sequential regimen with 200 mg for 12 to 14 days per month.

[e]Continuous combined or sequential regimens.

[f]Continuous combined regimen with 2.5 mg daily or sequential regimen with 5 mg for 12 to 14 days per month.

[g]Continuous combined regimen with 10 mg daily or sequential regimen with 20 mg for 12 to 14 days per month.