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A review of new evidence on risks of synthetic progestins in menopausal women at average risk for breast cancer, advantages of avoiding oophorectomy in women at average risk for ovarian cancer undergoing benign hysterectomy, and trends in estrogen therapy use in surgically menopausal women

IN THIS ARTICLE

This year's Menopause Update focuses on 2 menopause-related issues relevant to ObGyns and our menopausal patients:

- choosing the safest regimens, particularly with respect to risk of breast cancer, when prescribing hormone therapy (HT) to menopausal women
- reviewing the risks and benefits of premenopausal bilateral salpingo-oophorectomy and the pros and cons of replacement HT in surgically menopausal patients.

We hope that you find this updated information useful as you care for menopausal women.

Revisiting menopausal HT and the risk of breast cancer: What we know now

Abenhaim HA, Suissa S, Azoulay L, et al. Menopausal hormone therapy formulation and breast cancer risk. Obstet Gynecol. 2022;139:1103-1110. doi: 10.1097/AOG.0000000000004723.

Reevaluation of the Women's Health Initiative randomized controlled trials (WHI RCTs), long-term (median follow-up more than 20 years) cumulative follow-up data, and results from additional studies have suggested that estrogen therapy (ET) alone in menopausal women with prior hysterectomy does not increase the risk of breast cancer. By contrast, estrogen with progestin (synthetic progestogens that include medroxyprogesterone acetate [MPA] and

Prescribing progesterone as part of combination menopausal hormone therapy: Practical considerations

Progesterone capsules, available in generic form in 100-mg and 200-mg doses, are formulated with peanut oil, and they should be taken at bedtime as progesterone can induce drowsiness.

When combined with standard-dose estrogen, including oral estradiol 1.0 mg, transdermal estradiol 0.05 mg, or oral conjugated equine estrogen 0.625 mg, the appropriate dose of progesterone is 100 mg if used continuously or 200 mg if used as cyclic therapy. With higher doses of estrogen, progesterone 200 mg should be taken continuously.

An oral formulation that combines estradiol 1 mg and progesterone 100 mg does not contain peanut oil and, accordingly, can be used safely by those with peanut allergies. This combination product is marketed under the name Bijuva (TherapeuticsMD, Boca Raton, Florida).[1]

Reference

1. Lobo RA, Archer DF, Kagan R, et al. A 17β-estradiol-progesterone oral capsule for vasomotor symptoms in postmenopausal women: a randomized controlled trial. *Obstet Gynecol.* 2018;132:161-170. doi: 10.1097/AOG.0000000000002645. Erratum in: *Obstet Gynecol.* 2018;132:786.

norethindrone acetate) slightly increases the risk of breast cancer. In the past 10 years, several publications have shed light on whether the type of progestogen affects the risk of breast cancer and can help provide evidence-based information to guide clinicians.

Breast cancer risk with combined HT and synthetic progestin

In the first part of the WHI RCT, women were randomly assigned to receive either conjugated equine estrogen (CEE) plus synthetic progestin (MPA) or a placebo. Combined estrogen-progestin therapy (EPT) was associated with a modestly elevated risk of breast cancer.[1] In the second part of the WHI trial, CEE only (estrogen alone, ET) was compared with placebo among women with prior hysterectomy, with no effect found on breast cancer incidence.[2]

Most older observational studies published in 2003 to 2005 found that neither CEE nor estradiol appeared to increase the risk of breast cancer when used alone.[3-5] However, estrogen use in combination with synthetic progestins (MPA, norethindrone, levonorgestrel, and norgestrel) has been associated with an increased risk of breast cancer,[4,6] while the elevated risk of breast cancer with micronized progesterone has been less substantial.[7,8]

Newer data suggest the type of progestogen used affects risk

In a report published in the June 2022 issue of *Obstetrics and Gynecology,* Abenhaim and colleagues used a nested population-based case-control study of administrative data available in the UK Clinical Practice Research Datalink and provider prescriptions to evaluate the additive effect on the risk of breast cancer of the type of progestogen (micronized progesterone or synthetic progestins) when combined with estradiol for the treatment of menopausal symptoms.[9] A cohort of 561,379 women was included in the case-control study (10:1 ratio), 43,183 in the case group (patients diagnosed with invasive breast cancer), and 431,830 in the matched control group.

Overall, in the stratified analysis, a small but significant increase in the risk of breast cancer was found in ever users of menopausal HT (odds ratio [OR], 1.12; 95% confidence interval [CI], 1.09–1.15). Neither estradiol (OR, 1.04; 95% CI, 1.00–1.09) nor CEE (OR, 1.01; 95% CI, 0.96–1.06) was associated with an elevated risk of being diagnosed with invasive breast cancer. Of note, no elevated risk of breast cancer was associated with combination estrogen-progesterone therapy. However, the risk of breast cancer for women who had used synthetic progestins, mostly MPA, was significantly elevated (OR, 1.28; 95% CI, 1.22–1.35). Notably, this modestly elevated odds

FAST TRACK

In a stratified analysis of a nested population-based study of administrative data, Abenhaim and colleagues found a small but significant increase in the risk of breast cancer in ever users of menopausal HT. Notably, no elevated risk of breast cancer was associated with combination estrogen-progesterone therapy.

ratio with the use of estrogen-progestin HT is almost identical to that observed with CEE/MPA in the WHI.[1] Similar findings were found in women aged 50 to 60 years.

The adjusted analyses from the large WHI RCTs provide additional support: the synthetic progestin MPA combined with CEE showed a higher risk of breast cancer than CEE alone in women with prior hysterectomy.[10]

In the long-term follow-up of the WHI RCTs, after a median of 20.3 years postrandomization, prior randomization to CEE alone for postmenopausal women with prior hysterectomy was associated with a significantly lowered risk of breast cancer incidence and mortality.[11] By contrast, prior randomization to CEE plus MPA (EPT) for women with an intact uterus was associated with a small but significantly increased incidence of breast cancer but no significant difference in breast cancer mortality.

In the French E3N EPIC population-based prospective cohort study, Fournier and colleagues[4,5] found that women who received estrogen combined with synthetic progestins (mostly MPA) had a higher risk of breast cancer, with an age-adjusted relative risk of 1.4 (95% CI, 1.2–1.7), a finding not seen in women who received estrogen combined with micronized progesterone, similar to findings by Cordina-Duverger and colleagues and Simin and colleagues.[12,13] In the E3N study, only 948 women were identified with breast cancer; 268 of these had used synthetic progestins.[4,5]

Both the Abenhaim cohort[9] and the long-term outcomes of WHI RCT trial data[11] found a significant contributing effect of MPA (synthetic progestin) in the risk of breast cancer. Progestogens are not thought to exert a class effect. Although it is clear that progestogens (progesterone or progestins) prevent estrogen-induced endometrial neoplasia when dosed adequately, different types of progestogens have a differential risk of breast epithelium proliferation and carcinogenic potential.[14] A systematic review by Stute and colleagues found that micronized progesterone did not appear to alter mammographic breast density assessments or breast biopsy results.[15]

FAST TRACK

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Race considerations

The study by Abenhaim and colleagues was unable to address the issues of race or ethnicity.[9] However, in the racially diverse WHI trial of women with prior hysterectomy, estrogen-alone use significantly reduced breast cancer incidence in *all* participants.[10,16] Post hoc analysis of the 1,616 Black women with prior hysterectomy in the WHI RCT showed a significantly decreased breast cancer incidence with use of estrogen alone (hazard ratio [HR], 0.47; 95% CI, 0.26–0.82).[1] When race was evaluated in the long-term cumulative follow-up of the WHI trial, estrogen-alone use significantly reduced breast cancer incidence in Black women, with no adverse effect on coronary heart disease, global index, or all-cause mortality, and with fewer cases of venous thromboembolism.[17] The global index findings were favorable for Black women in their 50s and those with vasomotor symptoms.

Impact of HT in women with an elevated risk of breast cancer

Abenhaim and colleagues could not evaluate the effect of HT in women with a baseline elevated risk of breast cancer.[9] For these women, HT may be recommended after premature surgical menopause due to increased risks for coronary heart disease, osteoporosis, genitourinary syndrome of menopause, and cognitive changes when estrogen is not taken postsurgery through to at least the average age of menopause, considered age 51.[18,19]

Marchetti and colleagues reviewed 3 clinical trials that assessed breast cancer events in 1,100 *BRCA* gene mutation carriers with intact breasts who underwent risk-reducing salpingo-oophorectomy (RRSO) who used or did not use HT.[20] For *BRCA1* and *BRCA2* mutation carriers who received HT after RRSO, no elevated risk of breast cancer risk was seen (HR, 0.98; 95% CI, 0.63–1.52). There was a nonsignificant reduction in breast cancer risk for the estrogen-alone users compared with EPT HT (OR, 0.53; 95% CI, 0.25–1.15). Thus, short-term use of HT, estrogen alone or EPT, does not appear to

elevate the risk of breast cancer after RRSO in these high-risk women.

Individualizing HT for menopausal symptoms

The data presented provide reassuring evidence that longer-term use of ET does not appear to increase breast cancer risk, regardless of the type of estrogen (CEE or estradiol).[4,5,9,11] For women with a uterus, micronized progesterone has less (if any) effect on breast cancer risk. By contrast, the use of synthetic progestins (such as MPA), when combined with estrogen, has been associated with a small but real increased breast cancer risk.

The most evident benefit of HT is in treating vasomotor symptoms and preventing bone loss for those at elevated risk in healthy women without contraindications who initiate systemic HT when younger than age 60 or within 10 years of menopause onset. Benefit and risk ratio depends on age and time from menopause onset when HT is initiated. Hormone therapy safety varies depending on type, dose, duration, route of administration, timing of initiation, and whether, and type, of progestogen is used. Transdermal estradiol, particularly when dosed at 0.05 mg or less, has been shown to have less thrombotic and stroke risk than oral estrogen.[21]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

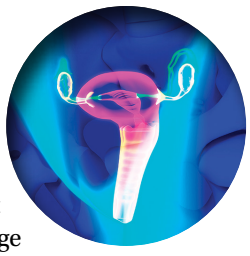
We can replace fear of HT with evidence-based discussions.[22] For women with prior hysterectomy who have menopausal symptoms that impact their quality of life, ET at menopause does not appear to increase the risk of breast cancer. For women with an intact uterus who are considering use of estrogen and progestogen, extended-duration use of combination HT with synthetic progestins slightly elevates the risk of breast cancer, while the use of micronized progesterone does not appear to elevate breast cancer risk. Likewise, transdermal estrogen does not appear to elevate thrombosis risk.

Individualizing treatment includes using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of benefits and risks of continuing or discontinuing HT or changing to lower doses. ObGyns who follow best practices in prescribing systemic HT can now help menopausal patients with bothersome symptoms take advantage of systemic HT's benefits while providing reassurance regarding menopausal HT's safety.[18] Transdermal therapy is a safer option for women at elevated baseline risk of venous thrombosis (for example, obese women) and older patients. Likewise, given its safety with respect to risk of breast cancer, the use of micronized progesterone over synthetic progestins should be considered when prescribing EPT to women with an intact uterus.

FAST TRACK

The data provide reassuring evidence that longer-term use of ET does not appear to increase breast cancer risk, regardless of the type of estrogen

Benefits of avoiding BSO in women at average risk of ovarian cancer



Erickson Z, Rocca WA, Smith CY, et al. Time trends in unilateral and bilateral oophorectomy in a geographically defined American population. Obstet Gynecol. 2022;139:724-734. doi: 10.1097/AOG.0000000000004728.

In 2005, gynecologist William Parker, MD, and colleagues used modeling methodology to assess the long-term risks and benefits of performing bilateral salpingo-oophorectomy (BSO) at the time of hysterectomy for benign disease in women at average risk for ovarian cancer.[23] They concluded that practicing ovarian conservation until age 65 increased women's long-term survival. Among their findings were that women with BSO before age 55 had an 8.6% excess overall mortality by age 80, while those with oophorectomy before age 59 had 3.9% excess mortality. They noted a sustained, but decreasing,

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mortality benefit until the age of 75 and stated that at no age did their model suggest higher mortality in women who chose ovarian conservation. Parker and colleagues concluded that ovarian conservation until at least age 65 benefited long-term survival for women at average risk for ovarian cancer when undergoing hysterectomy for benign disease.[23]

Certain risks decreased, others increased

A second report in 2009 by Parker and colleagues from the large prospective Nurses' Health Study found that, while BSO at the time of hysterectomy for benign disease was associated with a *decreased* risk of breast and ovarian cancer, BSO was associated with an *increased* risk of all-cause mortality, fatal and nonfatal coronary heart disease, and lung cancer.[24] Similar to the findings of the 2005 report, the authors noted that in no analysis or age group was BSO associated with increased survival. They also noted that compared with those who underwent BSO before age 50 and used ET, women with no history of ET use had an approximately 2-fold elevated risk of new onset coronary heart disease (HR, 1.98; 95% CI, 1.18–3.32).[24]

In 2007, Walter Rocca, MD, a Mayo Clinic neurologist with a particular interest in the epidemiology of dementia, and colleagues at the Mayo Clinic published results of a study that assessed a cohort of women who had undergone unilateral oophorectomy or BSO prior to the onset of menopause.[25] The risk of cognitive impairment or dementia was higher in these women compared with women who had intact ovaries (HR, 1.46; 95% CI, 1.13-1.90). Of note, this elevated risk was confined to those who underwent oophorectomy before 49 years of age and were not prescribed estrogen until age 50 or older.[25]

In a subsequent publication, Rocca and colleagues pointed out that BSO prior to menopause not only is associated with higher rates of all-cause mortality and cognitive impairment but also with coronary heart disease, parkinsonism, osteoporosis, and other chronic conditions associated with

aging, including metabolic, mental health, and arthritic disorders.[26]

Oophorectomy trends tracked

Given these and other reports[27] that highlighted the health risks of premenopausal BSO in women at average risk for ovarian cancer, Rocca and colleagues recently assessed trends in the occurrence of unilateral oophorectomy or BSO versus ovarian conservation among all women residing in the Minnesota county (Olmsted) in which Mayo Clinic is located, and who underwent gynecologic surgery between 1950 and 2018.[28]

The investigators limited their analysis to women who had undergone unilateral oophorectomy or BSO between ages 18 and 49 years (these women are assumed to have been premenopausal). The authors considered as indications for oophorectomy primary or metastatic ovarian cancer, risk-reducing BSO for women at elevated risk for ovarian cancer (for example, strong family history or known *BRCA* gene mutation), adnexal mass, endometriosis, torsion, and other benign gynecologic conditions that included pelvic pain, abscess, oophoritis, or ectopic pregnancy. When more than 1 indication for ovarian surgery was present, the authors used the most clinically important indication. Unilateral oophorectomy or BSO was considered not indicated if the surgery was performed during another primary procedure (usually hysterectomy) without indication, or if the surgeon referred to the ovarian surgery as elective.

Results. Among 5,154 women who had oophorectomies between 1950 and 2018, the proportion of these women who underwent unilateral oophorectomy and BSO was 40.6% and 59.4%, respectively.

For most years between 1950 and 1979, the incidence of unilateral oophorectomy was higher than BSO. However, from 1980 to 2004, the incidence of BSO increased more than 2-fold while the incidence of unilateral surgery declined. After 2005, however, both types of ovarian surgery declined. During the years 2005–2018, a marked decline in BSO occurred, with the reduced incidence in premenopausal BSO most notable among women undergoing hysterectomy or those without an indication for oophorectomy.

Historically, ObGyns were taught that the benefits of removing normal ovaries (to prevent ovarian cancer) in average-risk women at the time of hysterectomy outweighed the risks. We agree with the authors' speculation that beginning with Parker's 2005 publication,[23] ObGyns have become more conservative in performing unindicated BSO in women at average risk for ovarian cancer, now recognizing that the harms of this procedure often outweigh any benefits.[28]

Women with *BRCA1* and *BRCA2* gene mutations are at elevated risk for ovarian, tubal, and breast malignancies. In this population, risk-reducing BSO dramatically lowers future risk of ovarian and tubal cancer.

Data addressing the effect of RRSO in *BRCA1* and *BRCA2* gene mutation carriers continue to be evaluated, with differences between the 2 mutations, but they suggest that the surgery reduces not only ovarian cancer and tubal cancer but also possibly breast cancer.[29]

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Many of our patients are fearful regarding the possibility that they could be diagnosed with breast or ovarian cancer, and in their minds, fears regarding these 2 potentially deadly diseases outweigh concerns about more common causes of death in women, including cardiovascular disease. Accordingly, counseling women at average risk for ovarian cancer who are planning hysterectomy for benign indications can be challenging. In recent years, ObGyns have increasingly been performing opportunistic bilateral salpingectomy (OS) in women at average risk of ovarian cancer at the time of hysterectomy for benign disease. It is important to note that the studies we refer to in this Update addressed BSO, not OS. We hope that the findings we have reviewed here assist clinicians in helping women to understand the risks and benefits associated with premenopausal BSO and the need to discuss the pros and cons of HT for these women before surgery.

FAST TRACK

After 2005, both unilateral oophorectomy and BSO declined, and during 2005-2018, a marked decline in BSO occurred, with the reduced incidence in premenopausal BSO most notable among women undergoing hysterectomy or those without an indication for oophorectomy

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Trends show decline in ET use in surgically menopausal women

Suzuki Y, Huang Y, Melamed A, et al. Use of estrogen therapy after surgical menopause in women who are premenopausal. Obstet Gynecol. 2022;139:756-763. doi: 10.1097/AOG.0000000000004762.

In addition to highlighting the risks associated with premenopausal BSO in women at average risk for ovarian cancer, the reports referred to above also underscore that the use of replacement menopausal HT in premenopausal women who undergo BSO prevents morbidity and mortality that otherwise accompanies surgical menopause. In addition, the North American Menopause Society (NAMS) recommends replacement menopausal HT in the setting of induced early menopause when no contraindications are present.[18]

To assess the prevalence of HT use in surgically menopausal women, investigators at Columbia University College of Physicians and Surgeons used a national database that captures health insurance claims for some 280 million US patients, focusing on women aged 18 to 50 years who underwent BSO from 2008 to 2019.[30] The great majority of women in this database have private insurance. Although the authors used the term *estrogen therapy* in their article, this term refers to systemic estrogen alone or with progestogen, as well as vaginal ET (personal communication with Jason Wright, MD, a coauthor of the study, May 19, 2022). In this Update section, we use the term *HT* to include use of any systemic HT or vaginal estrogen.

Prevalence of HT use changed over time period and patient age range

Among almost 61,980 evaluable women who had undergone BSO (median age, 45 years; 75.1% with concomitant hysterectomy;

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median follow-up time, 27 months), with no history of gynecologic or breast cancer, HT was used within 3 years of BSO by 64.5%. The highest percentage of women in this cohort who used HT peaked in 2008 (69.5%), declining to 58.2% by 2016. The median duration of HT use was 5.3 months. The prevalence of HT use 3 years after BSO declined with age, from 79.1% in women aged 18–29 to 60.0% in women aged 45–50.[30]

This report, published in the June 2022 issue of *Obstetrics and Gynecology,* makes several sobering observations: Many surgically menopausal women aged 50 years and younger are not prescribed HT, the proportion of such women receiving a prescription for HT is declining over time, and the duration of HT use following BSO is short. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

As ObGyn physicians, we can play an important role by educating healthy women with induced menopause who are younger than the average age of spontaneous menopause, and who have no contraindications, that *the benefits of HT far outweigh risks*. Many of these women will benefit from longer-term HT, using doses substantially higher than are used in women who undergo spontaneous menopause.[31,32] After reaching the age of menopause, healthy women without contraindications may continue to benefit from HT into their 50s or beyond if they have vasomotor symptoms, bone loss, or other indications for treatment.[18,19]

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