*Menopause: The Journal of The North American Menopause Society*
Vol. 28, No. 1, pp. 000-000
DOI: 10.1097/GME.0000000000001680


# EDITORIAL

# Surgical menopause: health implications and hormonal management

*Andrew M. Kaunitz, MD, FACOG, NCMP,[1] and Stephanie Faubion, MD, FACP, NCMP[2]*

After Cesarean birth, hysterectomy represents the most common major procedure performed in US women.[1] A 2015 publication used a single US state database that included almost 7,000 US women undergoing hysterectomy for benign indications. Among women <51 years of age, bilateral salpingo-oophorectomy (BSO) with histologically normal ovaries found upon pathology evaluation was performed in nearly one of every four of these women.[2]

In contrast with natural menopause, surgical menopause (BSO before the natural age of menopause) causes a rapid drop in systemic estradiol.[3] There is confusion among women, and some clinicians regarding the term ''surgical menopause.'' It often helps to clarify that the absence of bleeding that occurs subsequent to hysterectomy does not mean the woman is menopausal. It is the absence of ovarian function after BSO which equates with surgical menopause. Among women with surgical menopause, short-term consequences include more severe vasomotor symptoms, and higher rates of mood disorders, sleep disturbances, sexual dysfunction, and joint symptoms, as well as reduced quality of life compared to women who undergo natural menopause.[4] However, the impact of surgical menopause also includes important long-term adverse health outcomes.

The best quality evidence regarding the long-term health consequences of surgical menopause comes from three large observational studies—two conducted in the United States and one in Britain. The prospective cohort Nurses' Health Study (NHS) followed over 29,000 US women who had a hysterectomy for benign disease. In more than half of these women, hysterectomy was accompanied by BSO. The mean age at the time of surgery was 43.3 years and 46.8 years, respectively, in women who had ovarian conservation or BSO. During 24 years of follow-up, overall mortality and coronary heart disease (fatal plus nonfatal) occurred more often with BSO. In contrast, ovarian and breast cancers (along with mortality from these two cancers) occurred less often among women who underwent BSO. Each of these differences achieved statistical significance ($P < 0.05$). The investigators estimated that with an estimated life span of 35 years after surgery, one additional death occurred for every nine BSO surgeries performed. They also noted that among women younger than age 50 at the time of hysterectomy, BSO was associated with significantly increased overall mortality in women who had never used estrogen; this association was not observed among past or current estrogen users.[5,6]

The Mayo Clinic Cohort Study of Oophorectomy and Aging, based in a single Minnesota county in which the great majority of residents are white, was a population-based retrospective cohort study of 2,390 women who underwent unilateral or bilateral oophorectomy for benign disease. Among premenopausal women in this cohort who underwent oophorectomy, the median age at the time of surgery was 44 years. Following bilateral oophorectomy (performed at the time of hysterectomy in 95% of these women), members of this cohort were followed for a mean of 25 years. Women who had undergone oophorectomy were age-matched to a referent group of women who had not undergone oophorectomy. Overall, BSO was not associated with increased overall mortality. However, among women who underwent BSO before age 45 years, overall mortality was significantly higher. This increased mortality risk was primarily noted in women who had not used estrogen up to at least the age of 45 years. Unilateral oophorectomy was not associated with increased mortality.[7] Similarly, a follow-up study in the Mayo Clinic Cohort Study of Oophorectomy and Aging-2 showed that BSO before the age of 46 years was associated with accelerated accumulation of multimorbidity defined by 18 chronic conditions associated with aging, a finding that was stronger in those women who did not receive estrogen therapy to age 46 years.[8]

A retrospective cohort study used a national UK database to assess health consequences of over 113 thousand women aged 35 to 45 years who underwent hysterectomy for benign indications from 2004 to 2014. One-third of these women also underwent BSO at the time of hysterectomy. Women with ovarian conservation were less likely to be hospitalized for coronary heart disease than women in the BSO group. Likewise, ovarian conservation was associated with fewer admissions for any cancer diagnosis as well as lower overall mortality. Each of these differences achieved statistical

Received September 11, 2020; revised and accepted September 11, 2020.
From the [1]University of Florida College of Medicine-Jacksonville, Jacksonville, FL; and [2]Mayo Clinic, Jacksonville, FL.
Funding/support: None reported.
Financial disclosure/conflicts of interest: Dr. Andrew Kaunitz has served on Advisory Boards for Mithra and Pfizer. The University of Florida receives research funding from Mithra.
Address correspondence to: Andrew M. Kaunitz, MD, FACOG, NCMP, 653-1 W. 8th St., Jacksonville, FL 32209. E-mail: andrew.kaunitz@jax.ufl.edu

significance ($P < 0.001$). In addition, the British investigators noted significantly fewer deaths from cancer ($P < 0.001$) and heart disease ($P = 0.002$) with ovarian conservation.[9]

Compared with natural menopause at the average age, early estrogen deprivation related to BSO is associated with an increased risk of neurologic disorders, including parkinsonism and cognitive decline.[10-12] A case-control study conducted by investigators at the Mayo Clinic observed that with neuroimaging, medial temporal lobe abnormalities are present in women who undergo BSO before menopause. These structural alterations in the brain may precede symptoms of dementia.[13]

Among the most bothersome sequelae of early surgical menopause are negative impacts on sexuality, including an elevated risk of genitourinary syndrome of menopause as well as hypoactive sexual desire disorder. The latter may result not only from the loss of ovarian androgen production but also from other factors including loss of fertility, mood problems and fear of entering a new relationship.[4,14]

In the current issue of this journal, Wong and colleagues review hysterectomies performed between 2016 and 2018 at six hospitals in Ontario with the goal of identifying nonindicated BSO. Appropriately, their criteria for this designation were age < 51 years, benign indications for hysterectomy and absence of endometriosis or pelvic adhesions. They found that overall, over two-thirds of BSO were indicated. However, the proportion of BSO that were indicated was higher in teaching hospitals and in surgeries performed by gynecologists with fellowship training in minimally invasive surgery.[15] These important observations underscore the role of clinician education in reducing nonindicated BSO in premenopausal women undergoing hysterectomy for benign disease.

With publication of initial findings from the Women's Health Initiative (WHI) hormone therapy (HT) trials in 2002, the prevalence of HT use among menopausal US women has plummeted.[16] This has led to menopausal women with bothersome symptoms not having access to clinicians knowledgeable about and willing to prescribe HT to appropriate candidates.[17] Unfortunately, post-WHI fears about the safety of HT have caused declines in HT use not only among symptomatic women with natural menopause but also among surgically menopausal women. In a 2011 cross-sectional analysis assessing the care of women who had undergone hysterectomy and BSO (mean age at surgery 44.3 y) at a teaching center in Western Canada, only 40% of patients were prescribed estrogen therapy postoperatively, and only one-third of women were using estrogen at the time they were interviewed for this study.[18]

Clinicians should recognize that findings from the Women's Health Initiative (WHI) do *not* apply to women <51 years of age with surgical menopause. In such women, in the absence of contraindications, HT (estrogen, with progestogen if a uterus is present) should be continued at least until age 51, the average age of menopause. This guidance is consistent not only with The North American Menopause Society's 2017 Hormone Therapy Position Statement (NAMS 2017) but also with experts in the field.[4,19-21]

Further, in women who experience premature (<age 40 y) or early (<age 45 y) menopause, higher estrogen doses aimed at achieving physiologic levels for a premenopausal woman (eg, oral micronized estradiol 2 mg, conjugated equine estrogen 1.25 mg daily, or transdermal estradiol 0.1 mg daily release rate) are recommended.[4,19-21]

An increasing number of young women with *BRCA* mutations placing them at high lifetime risk for ovarian and breast cancers are undergoing risk-reducing BSO. Often, these women are reluctant to use HT, and concerns regarding the safety of such therapy may deter some high-risk women from undergoing risk-reducing (and potentially lifesaving) BSO.[22] Although no randomized trials of menopausal HT in women with BRCA mutations have been conducted, a number of observational studies have examined the safety of estrogen therapy (following hysterectomy with BSO) or estrogen plus progestogen therapy (following BSO) in mutation carriers with intact breasts. Unfortunately, none of these studies include long-term follow-up. These observational studies, however, are consistent in noting that the use of HT in BRCA mutation carriers who have undergone risk-reducing BSO has not been associated with an elevated risk of breast cancer.[4] Although studies with long-term follow-up are needed, the findings of these observational studies should be included when counseling deleterious mutation carriers regarding risk-reducing BSO and subsequent use of HT, not only for menopausal symptom management, but also for mitigation of potential increased risk of adverse long-term effects on the bone, brain, and heart associated with early estrogen deprivation.

## REFERENCES


1. Novetsky AP, Boyd LR, Curtin JP. Trends in bilateral oophorectomy at the time of hysterectomy for benign disease. *Obstet Gynecol* 2011;118:1280-1286.
2. Karp NE, Fenner DE, Burgunder-Zdravkovski L, Morgan DM. Removal of normal ovaries in women under age 51 at the time of hysterectomy. *Am J Obstet Gynecol* 2015;213:716e711-716.
3. Lobo RA. Surgical menopause and cardiovascular risks. *Menopause* 2007;14 (3 pt 2):562-566.
4. Kingsberg SA, Larkin LC, Liu JH. Clinical effects of early or surgical menopause. *Obstet Gynecol* 2020;135:853-868.
5. Parker WH, Broder MS, Chang E, et al. Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 2009;113:1027-1037.
6. Parker WH, Feskanich D, Broder MS, et al. Long-term mortality associated with oophorectomy compared with ovarian conservation in the nurses' health study. *Obstet Gynecol* 2013;121:709-716.
7. Rocca WA, Grossardt BR, de Andrade M, Malkasian GD, Melton LJ 3rd. Survival patterns after oophorectomy in premenopausal women: a population-based cohort study. *Lancet Oncol* 2006;7:821-828.
8. Rocca WA, Gazzuola Rocca L, Smith CY, et al. Loss of ovarian hormones and accelerated somatic and mental aging. *Physiology (Bethesda)* 2018;33:374-383.
9. Mytton J, Evison F, Chilton PJ, Lilford RJ. Removal of all ovarian tissue versus conserving ovarian tissue at time of hysterectomy in premenopausal patients with benign disease: study using routine data and data linkage. *BMJ* 2017;356:j372.
10. Bove R, Secor E, Chibnik LB, et al. Age at surgical menopause influences cognitive decline and Alzheimer pathology in older women. *Neurology* 2014;82:222-229.

11. Phung TK, Waltoft BL, Laursen TM, et al. Hysterectomy, oophorectomy and risk of dementia: a nationwide historical cohort study. *Dement Geriatr Cogn Disord* 2010;30:43-50.
12. Rocca WA, Bower JH, Maraganore DM, et al. Increased risk of parkinsonism in women who underwent oophorectomy before menopause. *Neurology* 2008;70:200-209.
13. Zeydan B, Tosakulwong N, Schwarz CG, et al. Association of bilateral salpingo-oophorectomy before menopause onset with medial temporal lobe neurodegeneration. *JAMA Neurol* 2019;76: 95-100.
14. The North American Menopause Society (NAMS). The 2020 Genitourinary Syndrome of Menopause Position Statement of The North American Menopause Society. *Menopause*. 2020; 27:976-992.
15. Wong J, Murji A, Sunderji Z, et al. Avoidable bilateral salpingo-oophorectomy at the time of hysterectomy and potential for ovarian preservation. *Menopause* 2021;28:xxx-xxx.
16. Jewett PI, Gangnon RE, Trentham-Dietz A, Sprague BL. Trends of postmenopausal estrogen plus progestin prevalence in the United States between 1970 and 2010. *Obstet Gynecol* 2014;124:727-733.
17. Manson JE, Kaunitz AM. Menopause management—getting clinical care back on track. *N Engl J Med* 2016;374:803-806.
18. Chubaty A, Shandro MT, Schuurmans N, Yuksel N. Practice patterns with hormone therapy after surgical menopause. *Maturitas* 2011;69:69-73.
19. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2017; 24:728-753.
20. Faubion SS, Kuhle CL, Shuster LT, Rocca WA. Long-term health consequences of premature or early menopause and considerations for management. *Climacteric* 2015;18:483-491.
21. Pinkerton JV. Hormone therapy for postmenopausal women. *N Engl J Med* 2020;382:446-455.
22. Domchek S, Kaunitz AM. Use of systemic hormone therapy in BRCA mutation carriers. *Menopause* 2016;23:1026-1027.