

# Does BSO status affect health outcomes for women taking estrogen for menopause?

What do results from the Women's Health Initiative's 18-year follow-up study reveal?

**Q&A with JoAnn E. Manson, MD, DrPH, NCMP**

**D**o health effects of menopausal estrogen therapy differ between women with bilateral oophorectomy versus those with conserved ovaries? To answer this question a group of investigators performed a subanalysis of the Women's Health Initiative (WHI) Estrogen-Alone Trial,<sup>1</sup> which included 40 clinical centers across the United States. They examined estrogen therapy outcomes by bilateral salpingo-oophorectomy (BSO) status, with additional stratification by 10-year age groups in 9,939 women aged 50 to 79 years with prior hysterectomy and known oophorectomy status. In the WHI trial, women were randomly assigned to conjugated equine estrogens (CEE) 0.625 mg/d or placebo for a median of 7.2 years. Investigators assessed the incidence of coronary heart disease and invasive breast cancer (the trial's 2 primary end points), all-cause mortality, and a "global index"—these end points plus stroke, pulmonary embolism, colorectal cancer,

and hip fracture—during the intervention phase and 18-year cumulative follow-up.

OBG MANAGEMENT caught up with lead author JoAnn E. Manson, MD, DrPH, NCMP, to discuss the study's results.

## **OBG MANAGEMENT: How many women undergo BSO with their hysterectomy?**

**JoAnn E. Manson, MD, DrPH, NCMP:** Of the 425,000 women who undergo hysterectomy in the United States for benign reasons each year,<sup>2,3</sup> about 40% of them undergo BSO—so between 150,000 and 200,000 women per year undergo BSO with their hysterectomy.<sup>4,5</sup>

## **OBG MANAGEMENT: Although BSO is performed with hysterectomy to minimize patients' future ovarian cancer risk, does BSO have health risks of its own, and how has estrogen been shown to affect these risks?**

**Dr. Manson:** First, yes, BSO has been associated with health risks, especially when it is performed at a young age, such as before age 45. It has been linked to an increased risk of heart disease, osteoporosis, cognitive decline, and all-cause mortality. According to observational studies, estrogen therapy appears to offset many of these risks, particularly those related to heart disease and osteoporosis (the evidence is less clear on cognitive deficits).<sup>5</sup>



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*The author reports no financial relationships relevant to this article*

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### **OBG MANAGEMENT:** What did you find in your trial when you randomly assigned women in the age groups of 50 to 79 who underwent hysterectomy with and without BSO to estrogen therapy or placebo?

**Dr. Manson:** The WHI is the first study to be conducted in a randomized trial setting to analyze the health risks and benefits of estrogen therapy according to whether or not women had their ovaries removed. What we found was that the woman's age had a strong influence on the effects of estrogen therapy among women who had BSO but only a negligible effect among women who had conserved ovaries. Overall, across the full age range, the effects of estrogen therapy did not differ substantially between women who had a BSO and those who had their ovaries conserved.

However, there were major differences by age group among the women who had BSO. A significant 32% reduction in all-cause mortality emerged during the 18-year follow-up period among the younger women (below age 60) who had BSO when they received estrogen therapy as compared with placebo. By contrast, the women who had conserved ovaries did not have this significant reduction in all-cause mortality, or in most of the other outcomes on estrogen compared with placebo. Overall, the effects of estrogen therapy tended to be relatively neutral in the women with conserved ovaries.

Now, the reduction in all-cause mortality with estrogen therapy was particularly pronounced among women who had BSO before age 45. They had a 40% statistically significant reduction in all-cause mortality with estrogen therapy compared with placebo. Also, among the women with BSO, there was a strong association between the timing of estrogen initiation and the magnitude of reduction in mortality. Women who started the estrogen therapy within 10 years of having the BSO had a 34% significant reduction in all-cause mortality, and those who started estrogen more than 20 years after having their ovaries removed had no reduction in mortality.

### **OBG MANAGEMENT:** Do your data give support to the timing hypothesis?

**Dr. Manson:** Yes, our findings do support a timing hypothesis that was particularly pronounced for women who underwent BSO. It was the women who had early surgical menopause (before age 45) and those who started the estrogen therapy within 10 years of having their ovaries removed who had the greatest reduction in all-cause mortality and the most favorable benefit-risk profile from hormone therapy. So, the results do lend support to the timing hypothesis.

By contrast, women who had BSO at hysterectomy and began hormone therapy at age 70 or older had net adverse effects from hormone therapy. They posted a 40% increase in the global index—which is a summary measure of adverse effects on cardiovascular disease, cancer, and other major health outcomes. So, the women with BSO who were randomized in the trial at age 70 and older had unfavorable results from estrogen therapy and an increase in the global index, in contrast to the women who were below age 60 or within 10 years of menopause.

### **OBG MANAGEMENT:** Given your study findings, in which women would you recommend estrogen therapy? And are there groups of women in which you would advise avoiding estrogen therapy?

**Dr. Manson:** Current guidelines<sup>6,7</sup> recommend estrogen therapy for women who have early menopause, particularly an early surgical menopause and BSO prior to the average age at natural menopause. Unless the woman has contraindications to estrogen therapy, the recommendations are to treat with estrogen until the average age of menopause—until about age 50 to 51.

Our study findings provide reassurance that, if a woman continues to have indications for estrogen (vasomotor symptoms, or other indications for estrogen therapy), there is relative safety of continuing estrogen-alone therapy through her 50s, until age 60. For example, a woman who, after the average age of menopause continues to have vasomotor

### **FAST TRACK**

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symptoms, or if she has bone health problems, our study would suggest that estrogen therapy would continue to have a favorable benefit-risk profile until at least the age of 60. Decisions would have to be individualized, especially after age 60, with shared decision-making particularly important for those decisions. (Some women, depending on their risk profile, may continue to be candidates for estrogen therapy past age 60.)

So, this study provides reassurance regarding use of estrogen therapy for women in their 50s if they have had BSO. Actually, the women who had conserved ovaries also had relative safety with estrogen therapy until age 60. They just didn't show the significant benefits for all-cause mortality. Overall, their pattern of health-related benefits and risks was neutral. Thus, if vasomotor symptom management, quality of life benefits, or bone health effects are sought, taking hormone therapy is a quite reasonable choice for these women.

By contrast, women who have had a BSO and are age 70 or older should really avoid initiating estrogen therapy because it would follow a prolonged period of estrogen deficiency, or very low estrogen levels, and these women appeared to have a net adverse effect from initiating hormone therapy (with increases in the global index found).

**OBG MANAGEMENT: Did taking estrogen therapy prior to trial enrollment make a difference when it came to study outcomes?**

**Dr. Manson:** We found minimal if any effect in our analyses. In fact, even the women who did not have prior (pre-randomization) use of estrogen therapy tended to do well on estrogen-alone therapy if they were younger than age 60. This was particularly true for the women who had BSO. Even if they had not used estrogen previously, and they were many years past the BSO, they still did well on estrogen therapy if they were below age 60. ●

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