# Hormone replacement therapy in young women with surgical primary ovarian insufficiency

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Bilateral oophorectomy performed in women before they are menopausal induces surgical primary ovarian insufficiency, an acute and chronic deficiency of the hormones normally produced by the ovaries. Without hormone replacement therapy (HRT) most of these women develop severe symptoms of estrogen (E) deficiency and are at increased risk for osteoporosis, cardiovascular disease, cognitive decline, dementia, and the associated increases in morbidity and mortality. In cases in which a hysterectomy has been performed at the time of bilateral oophorectomy transdermal or transvaginal $E_2$ replacement therapy without cyclic progestin replacement is the optimum hormonal management for these women. There is substantial evidence this approach even reduces the risk for breast cancer. Unfortunately, unwarranted fear of all menopausal HRTs has become widespread following the reports of the Women's Health Initiative studies. This fear has led to a steep decline in use of E therapy, even in women in whom HRT is clearly indicated. Discussion of possible ovarian conservation in women who are premenopausal is an integral part of the preoperative planning for any women undergoing hysterectomy. Timely and effective HRT for women who will experience surgical primary ovarian insufficiency is clearly indicated. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

**Key Words:** Premenopausal oophorectomy, ovarian insufficiency, surgical menopause, estrogen therapy

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Most bilateral oophorectomies occur at the time of hysterectomy and most hysterectomies occur between ages 35 and 45 years, with more than half of all hysterectomies in women aged 45 years or younger (1, 2). As a result, surgical primary ovarian insufficiency (POI) is the leading cause of ovarian hormone deficiency in premenopausal women. Although the number of hysterectomies has declined in recent years, there are still >200,000 women who undergo bilateral oophorectomy each year in the United States (1, 2). This is the sum of surgeries done [1] at the time of hysterectomy, [2] bilateral oophorectomy performed for treatment of ovarian pathology, and [3] "stand-alone" procedures to reduce risk in women genetically predisposed to breast and ovarian cancer. Bilateral salpingo-oophorectomy essentially eliminates ovarian cancer risk and reduces breast cancer risk in these women (3).

The adverse effects of prophylactic oophorectomy are hormone deficiency-related symptoms, increased risk of acquiring certain diseases, and increased morbidity and mortality (4–6). These effects are similar to women who develop POI by other mechanisms. However, in Surgical POI symptoms are more sudden in onset and consequences can be more severe.

Before 2002 >90% of women used estrogen therapy (ET) after bilateral salpingo-oophorectomy. This was for good reason. ET started close to the time of surgery (6, 7) is effective in controlling symptoms, inhibiting disease processes, and reducing morbidity and mortality. At present, the figure has declined to <10%. For young women who have undergone oophorectomy, not taking E means years of loss of its protective effects. Nevertheless, fear of taking any kind of hormone therapy (HT) is pervasive despite the evidence for the safety and efficacy of ET (8).

Women undergoing natural menopause differ dramatically from women experiencing surgical menopause at a

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young age. In most cases women experiencing natural menopause have a gradual onset of ovarian hormone deficiency after prolonged intermittent and unpredictable ovarian function, inherent in the physiology of the process. Generally these women are treated with HT for symptoms, not as a replacement for missing ovarian hormones. This is the critical distinction for the clinician to keep in mind, and it is important to explain this to young women who will be undergoing bilateral oophorectomy.

## SYMPTOMS

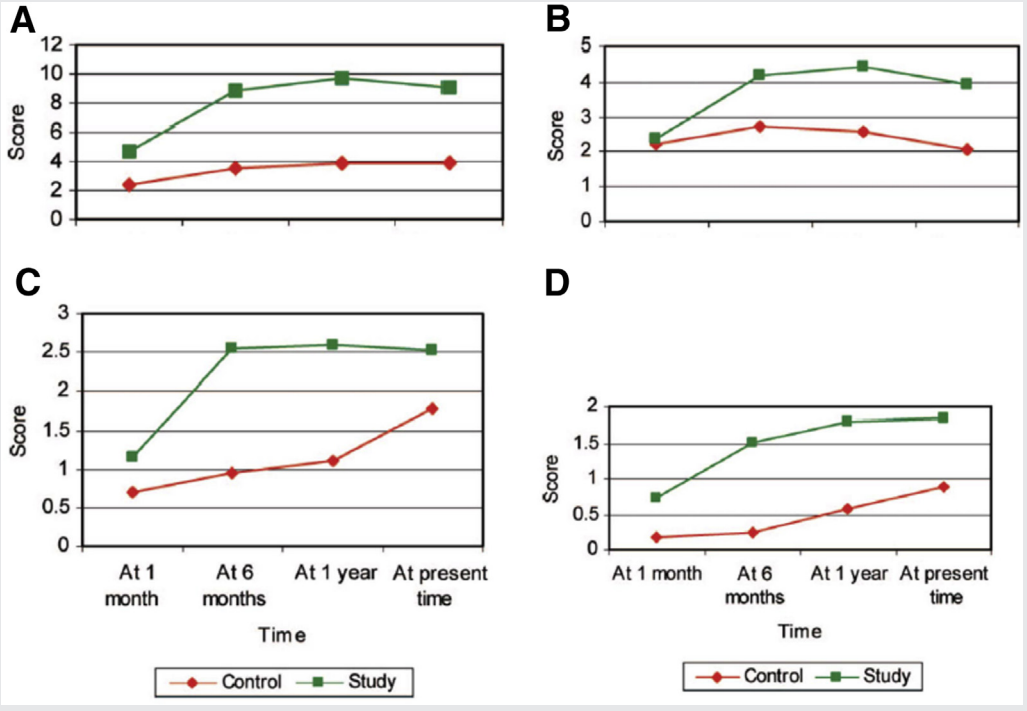
Women who develop surgical POI experience more severe and more frequent menopausal symptoms than women who experience natural menopause (9) (Fig. 1). These symptoms occur almost immediately and can persist for decades. Untreated, symptoms, such as hot flashes, sleep disturbance, fatigue, decreased sexual desire, anxiety and depressed mood, often have a major impact on quality of life, capacity to function, and disease risk (7,9–12). Also, delay in initiation of replacement E has an adverse effect on bone health (Table 1) (13).

Menopausal symptoms should be regarded as important signals of pathophysiological changes. Although androgen deficiency can contribute to these changes, most appear to be due to $E_2$ deficiency. For example, hot flashes are a state of vasomotor instability during which arterial flow is affected by surging levels of epinephrine and norepinephrine (12, 14). Vasodilation occurs in the skin as core blood flow shunts to the periphery. Coronary artery constriction during hot flashes can occur with >30% of women experiencing chest pressure or pain during a severe episode (12, 15). Vaginal dryness signals decreased genital blood flow and cell loss eventuating in genital atrophy and the urogenital syndrome of menopause (16). Impaired cognition, impaired short-term memory, sleep disturbance, and vasomotor instability reflect nervous system effects, including decreased brain blood flow and degenerative changes, predisposing to functional cognitive decline and dementia (11, 17, 18).

The impact of untreated menopausal symptoms on quality of life is seen in studies of the effects on symptomatic women in the workplace (19, 20). For example, 252,000 working women with untreated hot flashes were compared to asymptomatic age-matched women. During a 12-month period, the women with hot flashes showed increased work-loss, 1.1 million extra medical visits, and a health insurance bill almost $400,000,000 more compared to the asymptomatic women (19). A study of menopause symptoms and Dutch women concluded: "Over $^3/_4$ of women with severe menopausal symptoms report a low ability to undertake work" (20).

After bilateral oophorectomy, >80% of untreated women report one or more sex problems, including vaginal dryness with painful intercourse, inhibited sexual response, and loss of sexual desire (21–23). The increased occurrence of sexual dysfunction after bilateral salpingo-oophorectomy is more distressing in premenopausal than in postmenopausal women (23). Estrogen therapy has proved effective for

**FIGURE 1**




Symptoms compared as measured by the Greene Climacteric Scale between women experiencing natural menopause (Control) and women experiencing surgical primary ovarian insufficiency. (**A**) Psychological; (**B**) somatic; (**C**) vasomotor; (**D**) sexual function. Use with permission, Benshushan et al. (9).

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