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;106:1580–7. ©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

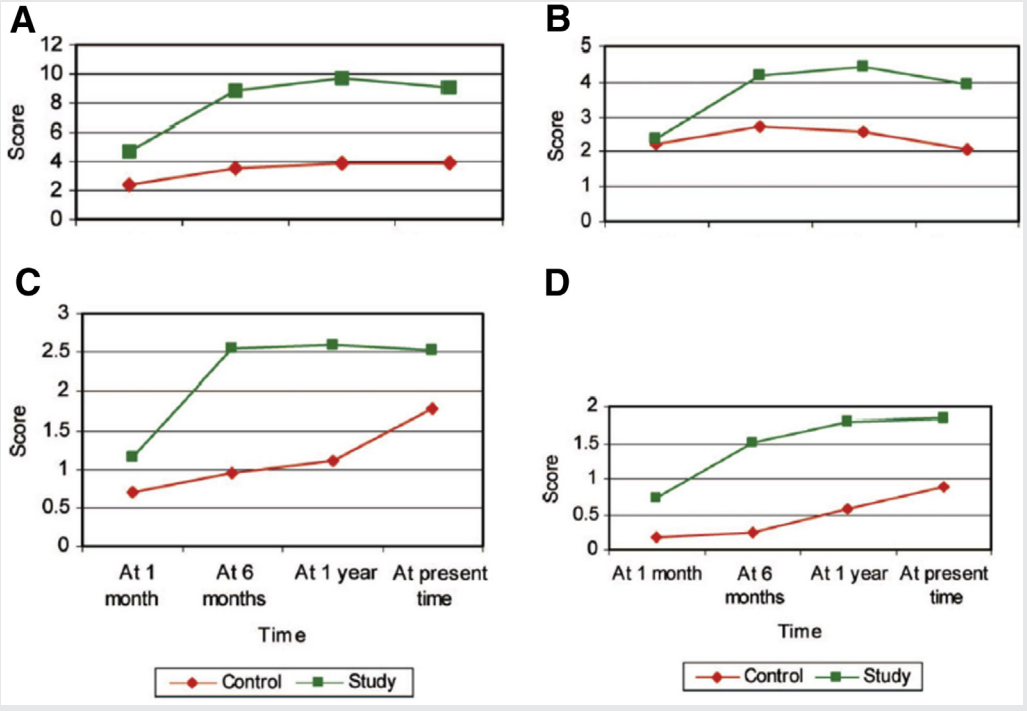
Women who develop surgical POI experience more severe and more frequent menopausal symptoms than women who experience natural menopause (9) (Fig. 1). These symptoms occur almost immediately and can persist for decades. Untreated, symptoms, such as hot flashes, sleep disturbance, fatigue, decreased sexual 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).

Sarrel. HRT in surgical POI. Fertil Steril 2016.

TABLE 1

Effect of delay in hormone replacement therapy on bone health in women undertaking bilateral risk reducing salpingo-oophorectomy.

Length of estrogen deprivation, mo	Age (y) at BRRSPO, median (range)	Age (y) at DEXA, median (range)	DEXA normal, n (%)	Osteopenia (DEXA T score −1.0 to −2.4), n (%)	Osteoporosis (DEXA T score < −2.4), n (%)
0	42.6 (31–48)	49 (41–61)	26 (84)	4 (13)	1 (3)
1–23	42.9 (34–48)	50 (32–68)	6 (60)	3 (30)	1 (10)
≥24	41.1 (24.9–48)	50 (38–78)	42 (54)	26 (33)	10 (13)

Note: BRRSPO = bilateral risk reducing salpingo-oophorectomy; DEXA = bone density scan. Used with permission, Challberg et al. (13).

Sarrel. HRT in surgical POI. Fertil Steril 2016.

restoring vaginal cytology and lubrication and, therefore, reducing the occurrence of dyspareunia (15). It is also effective in restoring sex response. However, the problem of loss of sexual desire may require the addition of an androgen to achieve satisfactory results (22, 23).

Severe vasomotor symptoms are associated with more frequent and more severe levels of depression and anxiety. For example, Kronenberg (12) reported depressed feelings during hot flashes were more common in women after surgical menopause than with natural menopause and that suicidal thoughts during hot flashes occurred almost twice as often (10%) in these women. With regard to hospitalization for attempted suicide, Rosenberg et al. (24) compared women who had experienced natural menopausal to women aged 35 years and younger who had undergone bilateral oophorectomy and had not used HT. They reported a relative risk of 2.4 for hospitalization for a suicide attempt in the women with surgical POI.

The pathophysiology that occurs with menopausal symptoms can contribute to subsequent disease risk. For example, The Study of Women's Health Across the Nation reported that hot flashes were associated with a higher incidence of insulin resistance and glucose levels (11). More recently, the investigators of the Study of Women's Health Across the Nation reported that severe hot flashes were "robustly" associated with higher intima media thickness, an important marker for subclinical cardiovascular disease (25). In the Women's Health Initiative (WHI) study, more frequent and more severe symptoms were associated with an increased risk of hypertension, cardiovascular disease, and stroke (7).

With regard to cardiovascular risk, there has been a paradigm shift in thinking with regard to effects of E deficiency on young women. Menopausal symptoms should be taken seriously and considered to be "canaries in the coal mine" signaling the need for medical attention and evaluation (26).

DISEASE

In the past, "symptoms" of hormonal insufficiency have been at the center of managing menopause. Evaluation and treatment focused on control of symptoms for a limited time with the expectation that once a woman passed through the menopausal transition there would be no further need for hormonal intervention. However, starting in the 1950s, as the cardiovascular and bone consequences of ovarian hormone deficiency became more apparent, the role of ovarian HT for the prevention of disease emerged. Subsequently, many cohort studies and randomized clinical trials have been carried out to determine the connection between loss of ovarian function and disease development, as well as the effects of hormone replacement in disease prevention. In this section, we describe the findings we believe are the most significant. We begin with the findings of the Mayo Clinic Cohort Study of Oophorectomy and Aging (5,6) because it addresses our focus on women who have undergone bilateral oophorectomy, and its findings relate to most of the concerns that have been raised by other studies about the immediate and long-term effects of ovarian hormone deficiency.

The Mayo Clinic Cohort Study of Oophorectomy and Aging (5, 6) reports that following bilateral oophorectomy risk is increased for all-cause mortality (28%), coronary heart disease (33%), stroke (62%), cognitive impairment (60%), parkinsonism (80%), osteoporosis and bone fractures (50%), sexual dysfunction (40%–110%), and, possibly, glaucoma. The study shows even greater risks with earlier age at the time of surgical POI. For example, all-cause mortality was increased by 67% in women who had undergone bilateral oophorectomy before age 45 years. Perhaps most important, the Mayo Clinic study indicates that starting ET at the time of oophorectomy and continuing until at least the age of natural menopause (ages 51–52 years) significantly reduces most, but not all, of the increased risks seen in untreated women. These findings support the so-called timing hypothesis that, applied to cardiovascular, bone, and nervous system protection, argues for hormone replacement as close to the onset of hormone deficiency as possible (27). Other studies besides the Mayo Clinic study, which show that starting ET as close to the time of surgery, optimizes cardiovascular protection, include the Danish Nurses Study, the WHI estrogen-only study, and the ELITE trial (6, 7, 28, 29). Most of these studies indicate the best cardiovascular results were in women who used E after oophorectomy for 10 years or more (6, 7, 28, 29).

For almost 70 years data have been accumulating that clarify the role of E_2 in disease prevention. Advances in molecular biology have enabled the identification of literally thousands of cellular actions of E_2 (30). Most of these data refer to actions that affect bone, and the circulatory, urogenital, and nervous systems. In addition, the clinical findings of E reducing risk for developing breast cancer can be explained by a variety of molecular mechanisms including E-induced apoptosis in breast cancer cells (30, 31).

CARDIOVASCULAR

In 1953, a Mayo Clinic autopsy study reported that 90% of the women with prior surgical POI showed severe atherosclerosis

cardiovascular disease (32). Among the women who had died before age 50 years, 50% had severe atherosclerotic disease. The youngest of the women, a 28-year-old developed surgical POI at age 23 years. The interval between oophorectomy and death averaged 11 years in the women who died before age 60 years. More than 80% of the women died before age 70 years (32). Hormone replacement therapy is not mentioned in the report but it is safe to assume that very few would have been treated hormonally during the years after their surgery.

Since that initial report, multiple mechanisms have been described through which E might inhibit atherosclerosis and maintains arterial function. These mechanisms include beneficial effects on cholesterol metabolism, direct actions in the arterial wall to inhibit atherosclerosis, and control of catecholamine release (33, 34).

We have already referred to the surges in catecholamine levels that occur with vasomotor symptoms and the correlation between these symptoms and risk for developing cardiovascular disease (11, 12, 14, 15). Estrogen modulation of catecholamine release helps to prevent coronary constriction, whereas E withdrawal may trigger arterial instability and spasm (15). Surges of catecholamine levels in reaction to E_2 depletion occur at various times in a woman's life most notably at menopause and when women stop ET. These surges have been associated with vasomotor instability, coronary spasm, myocardial infarction, and mortality (15, 35, 36).

Evidence regarding the role of E in slowing the atherosclerotic process is well documented in several trials (28,37,38). Using measures of arterial calcium, three separate studies show that E inhibits calcium deposition in coronary and carotid vessels as long as the intervention occurs within 3–6 years from the time of loss of ovarian function (28,37,38). In the National Institutes of Health Women's Health Initiative study (37), women who had not used E after developing surgical POI had more than a twofold risk of excess calcium in their arteries when they were enrolled in the study.

Multiple studies (29,39,40) have reported a heightened cardiovascular disease risk among women who developed surgical POI before age 50 years compared to women with natural menopause. For example, Ingelsson et al. (39) compared Swedish women after hysterectomy, with and without bilateral oophorectomy, with each other and with women who did not undergo surgery. The greatest risk for cardiovascular disease and stroke later in life was in the women who had undergone hysterectomy with bilateral oophorectomy. Although all women were <50 years, being younger at the time of surgical POI further increased the risks. Lokkegaard et al. (29) reported increased risk for ischemic heart disease in women aged 40–45 years who did not use HT for replacement after undergoing surgical POI. Among those who did use HT, there was no increase in ischemic heart disease. A meta-analysis (40) showed that ET has a greater effect in reducing cardiovascular disease risk after surgical compared with nonsurgical POI.

Diabetes is a major risk factor for cardiovascular disease. An increase in fasting insulin, glucose levels, and obesity is seen with menopause (41), and after the development of surgical POI there is an increase in insulin resistance (42). There are mixed findings regarding natural menopause and risk for diabetes. For surgical POI, however, the association with the development of diabetes and the metabolic syndrome appears to be more consistent. For example, the National Health and Nutrition Examination Survey/Epidemiologic Follow-up Study (43) studied the association between diabetes and hysterectomy, with or without bilateral oophorectomy in a cohort of 2,597 women. The average age for participants who had undergone hysterectomy with bilateral oophorectomy was 41.9 years. An increased risk for diabetes was restricted to women with both hysterectomy and surgical POI (hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.03–2.41). An earlier age of ovarian insufficiency, either natural or surgical, was associated with increased risk of diabetes, reaching an HR of 1.83 in women <40 years. The investigators concluded women with surgical POI "may represent a unique population with elevated risk for diabetes … and its potential complications" (43). A Norwegian national health study (44) found that women who had developed surgical POI as a result of risk-reducing bilateral oophorectomy had a significantly increased risk of metabolic syndrome compared with age-matched controls (47% vs. 36%; $P=.001$).

In contrast, the Diabetes Prevention Program (45) reported a lower diabetes risk among women who had experienced surgical POI compared with control premenopausal women. However, 88% of the women in that study received HT. Significantly, diabetes did not develop in any of the HT users during the course of the study.

BONE

There is an abundance of evidence linking bone loss to the E deficiency induced by natural menopause, which we will not review in the present article. Women who underwent surgical POI are at greater risk for bone loss and fracture compared with naturally menopausal women, likely due to the acute and abrupt onset of E and androgen deficiency (46). At 6 years after oophorectomy, almost twice the rate of bone loss has been seen in women who undergo surgical POI compared with women with natural menopause (47). If ET is started within 3 years of the onset of surgical POI the bone density is restored to preoperative levels. Starting ET at 6 years after the onset of surgical POI stopped bone loss but bone density was not restored to preoperative levels and stabilized at significantly lower levels (47). Mucowski et al. (48) reported decreased bone density in spine, hip, and femoral neck after surgical POI compared with postmenopausal women in whom the ovaries were not removed.

COGNITIVE DECLINE

A series of major studies show an increased risk for cognitive decline and dementia in women with surgical POI compared with women who experience natural menopause (18,49–52). Rocca et al. (49) showed that women who underwent unilateral or bilateral oophorectomy before natural menopause and were not treated with HRT had an increased risk of cognitive decline and dementia compared with a referent nonmenopausal control population (HR 1.46, 95% CI 1.13–1.90). Furthermore, the risk of cognitive decline

increased with younger age of oophorectomy, suggesting that increased duration of E deficiency may be a causal factor. Women who underwent bilateral oophorectomy before age 49 years and were given ET until at least age 50 years had no increased risk of dementia (50–52). Phung et al. (50) found an increased risk of dementia after bilateral oophorectomy performed before natural menopause, with younger age at oophorectomy exacerbating cognitive decline. Bove et al. (18) also demonstrated that earlier age of surgical menopause was associated with more rapid cognitive decline and increased Alzheimer disease neuropathology, in particular neuritic plaques. Their studies went on to show that HT, when initiated within 5 years of surgical POI and continued for at least 10 years, was associated with decreased decline in cognition but not in Alzheimer disease neuropathology.

In the Cache County Study (51), 85% of the women used ET after the onset of surgical POI. Among these women, those who started ET within 5 years of surgery and continued for more than 10 years, showed the greatest reduction in risk for developing Alzheimer disease (HR 0.62, 95% CI 0.42–0.92) (51). In an in-depth review Rocca et al. (52) conclude that premenopausal women undergoing surgical POI should initiate ET as close to the time of surgery as possible to maximize neuroprotective effects and reduce dementia risk. Based on their review, Rocca et al. (52) recommend ET for premenopausal women who underwent surgical POI to slow cognitive decline and reduce the risk for dementia and also recommend that ET should be continued until at least the age of natural menopause.

MOOD DISORDERS

The Mayo Clinic Cohort Study of Oophorectomy and Aging (53) reported that compared with age-matched women with intact ovaries women with onset of surgical POI before the clinical onset of natural menopause have higher rates of depression (HR 1.54, 95% CI 1.04–2.26) and anxiety (HR 2.29, 95% CI 1.33–3.95). The increase in symptoms occurred in women who had not suffered from depression or anxiety before their surgery. In this study (53), E use up to age 50 years did not modify the risk for depression or anxiety. A smaller Swedish study (54) compared women after hysterectomy whose ovaries were removed or retained and did or did not take ET. Anxiety and depression were significantly greater in women with surgical POI; ET significantly reduced the incidence and severity of the mood disorders among Swedish women with surgical POI.

Cohen et al. (55) reported that the risk for new onset depression is associated with more severe vasomotor symptoms. Three months of treatment with transdermal E_2 (0.100 mg/d) alleviated symptoms of depression and even led to remission when initiated in very early menopause (56).

No studies are available to specifically address the use of androgens for treatment of depression in women who underwent surgical POI. However, androgen replacement therapy in postmenopausal women has been shown to contribute to improved mood (57).

Not all studies report psychological disorders related to surgical POI. For example, the Study of Women Across the Nation (SWAN) (58) compared women with and without bilateral oophorectomy aged 42–52 years and found no increase in depression or anxiety levels.

MORTALITY

Many randomized clinical trials and cohort studies (6,59–61) indicate that surgical POI is a significant risk factor for all-cause mortality and that ET after surgery reduces the risk of mortality mostly by reducing cardiovascular events. Studies specifically indicating higher mortality risk in women with surgical POI, who did not use ET, include the Mayo Clinic Cohort Study of Oophorectomy and Aging and the Nurses Health Study.

The Mayo Clinic Cohort Study of Oophorectomy and Aging (5, 6) showed increased all-cause mortality of 67% in women who experienced surgical POI before age 45 years. Among these women, those who did not take E until the age of 45 years or later accounted for most of the mortality (HR 1.84, 95% CI 1.27–2.68) (59). Women who experienced surgical POI before age 45 years and used E until age 45 years or longer showed a reduced mortality risk compared with the referent women (HR 0.65, 95% CI 0.31–1.41) (59).

In the Nurses Health Study, women who experienced surgical POI before age 50 years and who did not use ET had a higher risk for all-cause mortality compared with women who did use E. Cardiovascular disease and stroke were responsible for most of the mortality. Women in the Nurses Health Study who had experienced surgical POI before age 50 years and never used ET showed an 85% increased risk for stroke and a 98% increased risk of coronary heart disease compared with women who did use ET. Among women with surgical POI before age 45 years and who did not use E experienced a significant increase in mortality rate compared with those who did (HR 1.44, 95% CI 0.67–0.99) (60).

A meta-analysis (61) of HT and total mortality in younger postmenopausal women (mean age, 54.5 years) included data from 19 randomized clinical trials and 8 prospective observational studies totaling >3,000,000 patient-years of surveillance. The mortality risk among E users was reduced by 28% when all data were combined.

Cessation of HRT after exiting research studies has been related to increased mortality. This may be mediated in part by increased catechol release related to vasomotor symptoms, and this having an adverse effect on vascular function. The observation is important because most studies include deaths within 30–90 days of study completion in the assigned treatment findings. For example, Mikkola et al. (36) reported increased cardiovascular mortality in the year immediately after HT withdrawal, with 25% of the deaths occurring in the first month. The Finnish group related these findings to surges of epinephrine, which occurred after hormone withdrawal.

Unfortunately, since the release of the WHI study results in 2002 many women with surgical POI who could have benefited by using ET have not done so. This may well be related to media reporting and unwarranted fear of using any form of menopausal HT, including an E-only regimen for women who have had a hysterectomy and require no progestin treatment. Regrettably, it has been estimated between

2002 and 2011 failure to take ET has caused almost 50,000 women with surgical POI to die prematurely (before age 70 years) (62).

E AND DECREASED RISK OF BREAST CANCER

Many factors have been identified that have led to avoidance of menopausal HT (62). Of these, fear of increased risk for breast cancer is the one most often cited. Whenever discussion about menopausal HT occurs, no matter how positive the findings fear of breast cancer frequently overshadows the good news. Essentially unnoticed are new concepts about HT and the protective effects of E in the breast (30, 31). The WHI study results, showing a statistically significant reduction in breast cancer risk in women who used ET after hysterectomy, have been confirmed in other randomized controlled trials including the Danish Osteoporosis Prevention Study (63, 64). In the WHI study and the Danish Osteoporosis Prevention Study, women using ET after hysterectomy compared with placebo showed more than a 20% reduced risk of developing breast cancer and more than a 60% reduced risk of dying of breast cancer. In the WHI study, almost 40% of the women had undergone bilateral oophorectomy before age 50 years, and all of the women in the Danish Osteoporosis Prevention Study who had undergone bilateral oophorectomy had their surgery at age 49 years or younger.

Of particular importance to women who have had risk-reducing bilateral oophorectomy are studies of women carrying *BRCA* mutations and who have used ET. These studies show no subsequent increase in the risk of developing breast cancer with use of ET (65–67). The National Institutes of Health-sponsored Two Sister Study is a case-control study among a cohort of sisters with and without breast cancer diagnosed before age 50 years. Among the sisters who used ET, there was a 42% lower risk for developing young-onset breast cancer (95% CI 0.34–0.99). Use of E plus progestin was likewise not associated with an increased risk of young-onset breast cancer in this population (68).

The mechanisms through which E acts to reduce breast cancer risk are discussed by Carroll et al. (30) and Chlebowski and Anderson (31). These investigators highlight the suppressive and apoptotic effects of E in breast cancer cells.

IMPROVING CARE FOR WOMEN WITH SURGICAL POI

Decreasing the frequency of bilateral oophorectomy at the time of hysterectomy in premenopausal women at low risk for ovarian cancer is one part of the solution to the problem of millions of women developing surgical POI and losing the protective effects of E at an age too young, and then failing to take ET (5, 61). Another part of the solution is to replace bilateral salpingo-oophorectomy with ovary-sparing bilateral salpingectomy (69). The effectiveness of bilateral salpingectomy in reducing risk for ovarian cancer is close to that of bilateral salpingo-oophorectomy, yet also reducing the harmful effects of acute and chronic E deficiency. The American College of Obstetrics and Gynecology has recommended ovarian conservation and bilateral salpingectomy in women aged 45 years or younger (70). These proposals have made some impact and a reduction in bilateral oophorectomy in women <45 years has occurred (1, 2). However, there is evidence that 20%–30% of conserved ovaries fail within 6 months to 3 years after simple hysterectomy or bilateral salpingectomy; these women should be regularly monitored for signs and symptoms of hormone deficiency (71–73).

A third part to the solution is to promote better understanding of the benefits of ET in women with surgical POI. The timing hypothesis underscores the urgency of encouraging women to start ET soon after oophorectomy—with the utmost urgency in the youngest women (5, 6, 28).

The dilemma is that, although data strongly support using ET in young women with surgical POI, societal factors overwhelm the findings and the steep decline in ET use in women with surgical POI continues (74). Complicating the issue, there is a lack of well-trained and experienced health care professionals able to deliver appropriate care for women with POI (75). However, the tide may be turning. New findings are too compelling to ignore; the most recent studies continue to show cardiovascular, bone, neurological, urogenital, and breast protection—especially in women who use ET immediately after the onset of surgical POI.

For premenopausal women who have had a hysterectomy and bilateral oophorectomy, the benefits of ET far outweigh risks and treatment can be life-preserving, and in some cases life-saving. The recommendation that ET be continued until the age of natural menopause (51–52 years) is based on the findings of efficacy and safety of E use to that age. However, there are significant findings that support continuing use of ET at least until the age of 60 years (28, 63, 64). Women with surgical POI who have hypoactive sexual desire may benefit from adding an androgen to their E-only treatment (76). Women who have undergone risk reduction bilateral oophorectomy with the uterus left in situ are in a different situation. Their treatment should be similar to that recommended for women who have experienced POI.

In summary, surgical POI is the most frequent cause of premenopausal ovarian hormone deficiency. Loss of ovarian hormone production induces symptoms that should be taken seriously. The symptoms affect quality of life, capacity to function at home and in the workplace, and are associated with disease development and increased mortality. Estrogen therapy effectively controls most of these symptoms and inhibits pathological processes that can lead to osteoporosis, atherosclerosis, dementia, and other disorders. Estrogen therapy is most beneficial when started at the time of oophorectomy and continued at least until age 50 years. Extension of ET, for symptom control and disease prevention, at least until the age of 60 years, is supported by the findings of the WHI E-only trial as well as other recent randomized clinical trials.

Perhaps the most significant reason women and clinicians fear and avoid ET is the mistaken belief that it increases their risk for developing breast cancer. In fact, ET does not increase breast cancer risk in premenopausal women including women who carry the *BRCA1* and *BRCA2* gene mutations.

It is unfortunate that fear of ET has led to widespread avoidance of its use. Facing this reality, some investigators

have advocated retention of ovaries at the time of hysterectomy in women age 45 years and younger to maintain the protective effects of ovarian hormones. Others have advocated bilateral salpingectomy with hysterectomy, a procedure that would greatly reduce ovarian cancer risk, yet still retaining the ovaries.

Facts about the safety and efficacy of ET should be used to help women and their clinicians overcome fears of HT. However, it is important to recognize that fear of HT has become deeply imbedded, publication of the positive findings for ET have had little impact, and the decline in use of ET continues.

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