

# Clinical Effects of Early or Surgical Menopause

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Increasing numbers of women experience early menopause due in part to surgical treatment for benign gynecologic disorders and the rise in risk-reducing bilateral salpingo-oophorectomy in women with *BRCA* mutations. Unfortunately, the adverse health consequences of early loss of ovarian function accelerate the menopausal state and affect multiple systems, including cardiovascular, neurologic, bone, and connective tissue, and affect quality of life owing to vasomotor symptoms, mood, sleep, and sexual function. Yet many clinicians and women remain reluctant to use hormone therapy because of the Women's Health Initiative's adverse findings, even though they are not applicable to women with early menopause. This review examines the effects of early menopause and highlights the critical role of hormone therapy in this population.

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There are many causes of early menopause (younger than age 45 years) or premature menopause (younger than age 40 years), including primary ovarian insufficiency, idiopathic disease, genetic disorders, autoimmune disorders, chemotherapy or pelvic radiation therapy, sur-

gical oophorectomy, and risk-reducing bilateral salpingo-oophorectomy (BSO) in women with the *BRCA* mutation. There are notable differences in spontaneous early menopause compared with menopause related to surgery or chemotherapy. Spontaneous early menopause is typically a gradual process. Surgical menopause is abrupt, with circulating ovarian hormones levels more substantially reduced than in natural menopause.<sup>1</sup>

Chemotherapy-induced menopause can be rapid or gradual depending on baseline ovarian reserve, gonadotoxicity, and duration of chemotherapy.<sup>2</sup> Regardless of cause, premature menopause and loss of estrogens and androgens before the normal age of menopause (median 51 years) affect a myriad of systemic functions and have long-term health consequences.

Premature menopause due to primary ovarian insufficiency occurs in approximately 1% of women,<sup>1</sup> and 5% of women enter natural menopause before age 45.<sup>3</sup> Despite the well-established health consequences of early menopause and American College of Obstetricians and Gynecologists guidance,<sup>4</sup> 23% of women aged 40–44 years and 45% of women aged 45–49 years undergo elective BSO with hysterectomy for benign disease.<sup>5–7</sup>

Early menopause is associated with short-term and long-term harmful health effects. Women with early menopause more often experience moderate to severe vasomotor symptoms (90% vs 70%), more severe sleep disturbance (odds ratio 2.13 surgical

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This article includes a discussion of off-label treatments for postmenopausal women with hypoactive sexual desire disorder, including systemic testosterone products, none of which are approved for women, and flibanserin and bremelanotide, which are approved only for premenopausal women. Systemic testosterone is also discussed as an off-label treatment for vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM). Systemic hormone therapy is discussed as an off-label therapy for treatment of mood disorders in postmenopausal women.

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menopause compared with natural menopause),<sup>8</sup> and reduced quality of life.<sup>9,10</sup>

Several long-term observational studies indicate that abrupt cessation of ovarian function before age 45 is associated with acceleration of cardiovascular changes, with higher risk of cardiovascular disease (CVD), cardiovascular mortality, stroke, and all-cause mortality.<sup>11</sup> Other systems affected include musculoskeletal changes (osteoporosis), neurocognitive changes (dementia and parkinsonism), psychiatric disorders (depression and anxiety), and urogenital changes associated with sexual dysfunction.<sup>12</sup>

The results of randomized trials of hormone therapy (HT) in older postmenopausal women cannot be generalized to women experiencing early menopause.<sup>13</sup> A 2019 subgroup analysis of the estrogen-only (conjugated equine estrogens) arm of the Women's Health Initiative of nearly 10,000 women with prior total abdominal hysterectomy (TAH)-BSO found that conjugated equine estrogens were associated with a reduction in all-cause mortality in younger women aged 50–59 years (hazard ratio [HR] 0.69, 95% CI 0.48–0.96) but not in older women aged older than 70 years (HR 1.02, 95% CI 0.86–1.21).<sup>14</sup>

This review highlights the health consequences and management of early menopause in average-risk women, the effect of risk-reducing options in women with *BRCA* mutations, particularly risk-reducing BSO, and the evidence supporting HT until the age of natural menopause.

## PATHOPHYSIOLOGY

The accepted definition of menopause is no menstrual bleeding for 12 consecutive months. In postmenopausal women, the estradiol (E2) level is consistently lower than 20 pg/mL, and the follicle-stimulating hormone (FSH) level is greater than 30 international units/L. However, serum levels are not typically used to define menopause. In women younger than 40 years of age, primary ovarian insufficiency is usually diagnosed when there has been amenorrhea for 3–6 months and two FSH levels in the menopausal range (eg, greater than 30 international units/L) measured 1 month apart.<sup>15</sup>

The physiologic mechanism(s) underlying short-term and long-term health changes in early menopause are linked to the significant decline in circulating ovarian E2 and androgen production. This tenet, first highlighted by Parker et al,<sup>16</sup> is recognized by most obstetrician-gynecologists. The predominant teaching in obstetrics and gynecology residency programs is to strongly consider conserving ovaries in women younger than 40–45 years of age and prophylactic BSO in women older than 55 years of age undergoing hyster-

ectomy for benign disease.<sup>17</sup> Women should be informed of the effect of BSO on sexual function regardless of age. One important reminder to practitioners is that removal of the uterus and tubes while conserving the ovaries can inadvertently affect ovarian blood flow and diminish future ovarian function. In a large cohort study of 406 women with hysterectomy with ovarian conservation, women with hysterectomy had a twofold higher risk of ovarian failure than women with intact uteri (HR 1.92, 95% CI 1.29–2.86).<sup>18</sup> Recent studies have detected changes in biomarkers of ovarian function such as antimüllerian hormone, FSH, and ultrasound Doppler flow studies.<sup>19,20</sup>

## VASOMOTOR SYMPTOMS AND QUALITY OF LIFE

Vasomotor symptoms, otherwise known as hot flashes and night sweats, are the hallmark symptoms of the menopause transition.<sup>21</sup> Vasomotor symptoms are one of the chief menopausal symptoms for which women seek medical treatment.<sup>22</sup> Up to 80% of women experience vasomotor symptoms during menopause, with a median duration of 7.4 years and an average of four to five hot flashes per day.<sup>21</sup>

The loss of ovarian hormones often results in more frequent and severe vasomotor symptoms after BSO than for natural menopause.<sup>23</sup> Hysterectomy with ovarian conservation is also associated with more severe vasomotor symptoms. A prospective study of women in Australia undergoing hysterectomy with ovarian conservation (before age 50 years) found a higher risk of experiencing vasomotor symptoms persisting for more than a decade,<sup>24</sup> perhaps due to disruption of ovarian blood flow after surgery. Studies of U.S. women demonstrate an effect of vasomotor symptoms on other key quality-of-life outcomes, including sleep, mood, and cognitive function.<sup>25</sup>

The Menopause Epidemiology Study, a population-based study of 2,073 U.S. women aged 40–65 years, evaluated the effect of vasomotor symptoms on health-related quality of life using the Menopause-Specific Quality of Life Questionnaire.<sup>26</sup> Results confirm the negative effects of menopausal symptoms on daily living and that younger age was associated with worse health-related quality of life. Women with primary ovarian insufficiency reported additional diminished quality of life in other domains associated with poor psychosocial functioning.<sup>27</sup>

## METABOLIC AND CARDIOVASCULAR HEALTH

A number of metabolic changes have been well characterized in the presence of long-term



hypoestrogenism. These include an increase in intra-abdominal adiposity without significant weight gain or changes in physical activity, an increase in abdominal circumference (waist/hip ratio), and an increase in total cholesterol levels.<sup>28</sup> Cohort studies of patients with risk-reducing BSO indicate an associated increased incidence of metabolic syndrome.<sup>29</sup> The vascular endothelium is a major hormonal target for estrogen. Experimental animal and human data indicate that estrogen mediates nitric oxide vasodilatation and preserves acetylcholine-mediated peripheral vasodilation.<sup>30</sup> Kalantaridou found that young women with primary ovarian insufficiency had significantly impaired vascular endothelial function that normalized with estrogen therapy, indicating the potential downstream effects of early menopause.<sup>31</sup>

The literature linking early loss of ovarian function with increased risk of CVD and death consists mainly of prospective, cohort, observational studies. As early as 1976, the Framingham study found that women without ovarian function in their 40s had an increased incidence of CVD compared with age-matched women in a control group. These results led to the initial hypothesis that estrogen is protective against CVD and explained the later onset of CVD in women compared with men.<sup>32</sup> In a more recent meta-analysis of almost 300,000 women examining age at onset of menopause and cardiovascular risk, women with early menopause had a greater relative risk (RR) for coronary heart disease (RR 1.5, 95% CI 1.28–1.76), fatal coronary heart disease (RR 1.11, 95% CI 1.03–1.31), and overall mortality (RR 1.12, 95% CI 1.03–1.21).<sup>11</sup> The National Heart, Lung, and Blood Institute's Multi-Ethnic Study of Atherosclerosis, a cohort of 3,000 women followed for 8.5 years, found that heart failure was 66% higher in women with early menopause compared with women with natural menopause (HR 1.66, 95% CI 1.01–2.73;  $P=.04$ ).<sup>33</sup>

The association of stroke and stroke mortality with early menopause is less clear. Muka et al report that stroke mortality remained unchanged for those with early menopause (RR 0.99, 95% CI 0.92–1.07).<sup>11</sup> In contrast, other observational studies have shown an increased risk of stroke, particularly ischemic stroke, in women with early menopause.<sup>34</sup>

Early surgical menopause is associated with early mortality, largely as a result of increased CVD that decreases with older age at BSO.<sup>35</sup> In a meta-analysis,<sup>36</sup> CVD incidence was found to be higher in women with menopause before age 50 and was highest among women with early BSO. The Mayo Clinic Cohort Study of Oophorectomy and Aging confirmed increased mortality in women with BSO before age 45 without HT.<sup>37</sup> The Nurses' Health Study found that

women who underwent BSO before age 50 and not on HT had a substantial increase in all-cause mortality, cancer mortality, and CVD mortality.<sup>38</sup> A recent meta-analysis of 15 observational studies of more than 300,000 women with natural menopause found that age affects the risk of CVD, with the highest risk with the earliest menopause. Compared with women with natural menopause at age 50–51 years, CVD risk was increased in women with very early menopause (younger than 40 years; HR 1.55, 95% CI 1.38–1.73), early menopause (40–44 years; HR 1.30, 95% CI 1.22–1.39), and relatively early menopause (45–49 years; HR 1.12, 95% CI 1.07–1.18).<sup>35</sup> Unfortunately, these changes are clinically silent, occur more than a decade after early menopause, and yet can be reduced or mitigated with appropriate use of HT.

## CONNECTIVE TISSUE, MUSCULOSKELETAL HEALTH, AND BONE HEALTH

A significant decline in circulating estrogen has major effects on skin, joint, muscle, and bone. Low estrogen levels are associated with accelerated skin aging from thinning, loss of collagen, reduced elasticity, increased wrinkling, and dryness.<sup>39</sup> These changes are partially reversible with exogenous estrogen.<sup>39</sup>

Arthralgias are common and reported in 50% of women during the menopause transition, although they are generally transient and not the predominant symptom.<sup>40,41</sup> Clinically, women who have abrupt-induced hypoestrogenism with gonadotropin-releasing hormone analogs report joint stiffness and muscle stiffness.<sup>42</sup> In a minority of women, arthralgias may persist and evolve into fibromyalgia, arthritis, osteoarthritis, or rheumatoid arthritis.<sup>39</sup> In the Women's Health Initiative, the estrogen-alone group had a significant reduction in joint pain compared with the placebo group (76.3% vs 79.2%,  $P=.001$ ) and significantly lower mean joint pain scores (1.16 [0.87] vs 1.22 [0.88],  $P<.001$ ).<sup>43</sup>

Bone turnover and the bone remodeling cycle are directly affected by estrogen. In the setting of low estrogen, bone resorption exceeds bone formation, causing a net bone loss. Bone density decreases by as much as 6.7% in premenopausal women after BSO.<sup>44</sup> During the first 3 years after menopause, bone density decreases by 2.4% per year and then declines to 1.2% annually. Bone density changes are greatest at the vertebral bodies, followed by changes at the hip, and can be monitored in patients with bone densitometry. Periodic bone densitometry measurements are recommended every 2 years beginning at age 65 years for average-risk women. Because bone density is an



indirect estimate of bone strength, fracture risk at both the vertebral spine and hip increases significantly in the absence of HT. Multiple clinical studies have established that the trajectory of ongoing bone loss is prevented with HT.<sup>45</sup>

## COGNITIVE FUNCTION AND NEUROLOGIC DISORDERS

At a neuronal cell level, a variety of critical biological effects have been associated with direct estrogen action through its receptors ER $\alpha$  and ER $\beta$ . Estrogen induces neurotrophic effects such as growth of dendritic spine synapses in the rat hippocampus and has neuroprotective effects in aging animal models.<sup>46</sup>

Both menopausal stage and menopause symptoms appear to influence cognitive function at midlife. Difficulty concentrating and remembering are common during the menopausal transition and in early postmenopause.<sup>47,48</sup> Anxiety is linked with slower processing speed and memory performance. Depression is associated with lower processing speed.<sup>49</sup> Sleep difficulties also are associated with poorer memory and attention.<sup>50</sup> In the Penn Ovarian Aging Study, verbal memory and processing speed declined significantly from the premenopausal stage to the postmenopausal stage.<sup>51</sup> Studies of pharmacologic suppression of E2 with gonadotropin-releasing hormone analogs demonstrate that estrogen contributes to memory function in younger women.<sup>52</sup>

Oophorectomy after natural menopause is generally not associated with a decline in cognitive performance.<sup>53</sup> In contrast, oophorectomy before the age of natural menopause is associated with cognitive impairment and dementia. The prospective Mayo Clinic Cohort Study of Oophorectomy and Aging found a twofold increased risk of cognitive impairment or dementia with early BSO, with a trend of higher risk with earlier age at BSO.<sup>54</sup> This increased risk was attenuated in women who received HT at least until age 50 years. A Danish cohort similarly found that early hysterectomy with BSO before age 50 years carried a greater risk of early-onset dementia (RR 2.33, 95% CI 1.44–3.77), with the risk correlating with earlier age at BSO.<sup>55</sup> Moreover, the greatest risk was associated with youngest age at BSO. Memory for verbal information may be compromised immediately after surgical menopause and in the longer term in women who undergo surgical menopause before the age of natural menopause. Small trials indicate that estrogen therapy can prevent declines in memory after surgical menopause in younger women,<sup>56,57</sup> providing evidence of estrogen's effect on memory function in younger women.<sup>52</sup>

Bove et al also found that early surgical menopause is associated with cognitive decline and that earlier age at menopause was associated with faster decline in cognition ( $P < .001$ ).<sup>58</sup> Surgical menopause was also associated with Alzheimer disease<sup>54</sup> neuropathology ( $P = .038$ ), specifically neuritic plaque formation ( $P = .013$ ), on postmortem brain pathology. Parkinson disease is increased in women with surgical menopause before the age of natural menopause, and HT does not attenuate this risk.<sup>59</sup>

## MOOD

The prevalence of depression in American women is estimated to be 10.4% for all adult women and 11.5% for women aged 40–59 years.<sup>60</sup> Theories exist as to why women have a twofold increased risk of developing depression compared with men. One concept, the “windows of vulnerability” for depression, referred to as reproductive-related depressive episodes, proposes an increased sensitivity in some women to changes in the hormonal milieu during the luteal phase of their cycles, the postpartum period, the menopause transition, or all of these.<sup>61</sup> Awareness of this sensitivity to the hormonal milieu is evident in guidelines to screen women for perinatal and postpartum mood disorders (prevalence: 11.9% for perinatal depression<sup>62</sup> and 13–19% for postpartum depression)<sup>63</sup> and the inclusion of premenstrual dysphoric disorder as a diagnostic category.<sup>64</sup>

Longitudinal studies demonstrate that depressive symptoms increase during the menopausal transition.<sup>65</sup> An analysis of 12 cross-sectional studies in perimenopausal and premenopausal women found that 45–65% of perimenopausal women report elevated depressive symptoms compared with 28–31% of premenopausal women.<sup>66</sup> Findings from InterLACE, which combined data from more than 230,000 midlife women across 20 cohort and cross-sectional studies,<sup>67</sup> confirm that depressive symptoms are strongly associated with vasomotor symptoms.<sup>68,69</sup> Prospective longitudinal studies, designed to address the association between menopause transition stage and depression, established that risk of major depression in the perimenopause compared with the premenopause is associated with a history of major depression.<sup>66</sup> However, cohort studies have documented a twofold to fourfold increased risk of major depression throughout the entire menopause transition and early postmenopausal years. Risk factors include demographic characteristics, somatic symptoms (eg, vasomotor symptoms, insomnia), health problems, mental health issues, psychosocial problems, stressful life circumstances, low social support, high trait anxiety, and CVD.<sup>68</sup>



The diagnosis of primary ovarian insufficiency is often unexpected and devastating. Suddenly being informed of infertility can result in depression and low self-esteem. Liao et al found that women with primary ovarian insufficiency have higher degrees of depression, poorer satisfaction with life, lower self-esteem, higher perceived stress, and lower sexual well-being than age-matched women in a control group.<sup>70</sup> Three major reasons emerge from the literature: infertility; menopausal symptoms, particularly vasomotor symptoms; and perceived lack of support from health care services.<sup>25</sup>

Early menopause with BSO is linked with an increased risk of depression and anxiety. A retrospective study found that women undergoing elective TAH with BSO who did not receive postsurgical HT had significantly higher anxiety and depression than women undergoing TAH alone.<sup>71</sup> A study of U.S. women undergoing hysterectomy between the ages of 31 and 49 years similarly found that women had significantly reduced emotional health at 24 months (using subscales of the Profile of Mood States) after TAH-BSO than women undergoing TAH alone.<sup>72</sup> The Mayo Clinic Cohort Study of Oophorectomy and Aging followed women for a median of 24 years after BSO, comparing them with an age-matched cohort in the general population. The study found an increased risk of new depression and new anxiety in women who underwent BSO, with an association of increased risk with younger age at BSO. In women who underwent BSO, HT did not ameliorate this risk.<sup>73</sup>

## SLEEP

Sleep disturbances are more common in women than men, and sleep quality deteriorates with age. These are among the most common symptoms for women in the perimenopause, with a prevalence of 40–56%. Vasomotor symptoms can interfere with sleep, but sleep disturbance may be independently present. In studies of specific sleep disturbances in perimenopausal women, 57% had difficulty staying asleep and 60.7% reported waking too early. The Study of Women Across the Nation confirms that vasomotor symptoms are associated with all aspects of sleep disturbance, including poor sleep continuity and quality (ie, falling asleep, staying asleep, and early morning awakening). Women with more frequent and severe vasomotor symptoms are more likely to have depressed mood that is largely explained by the associated sleep disturbances.<sup>74,75</sup> Surgical menopause is associated with more severe sleep disturbances than natural menopause.<sup>76</sup>

In longitudinal analyses conducted in both the Study of Women Across the Nation and the Penn Ovarian Aging Study, vasomotor symptoms were strongly associated with sleep problems, but reproductive hormone concentrations were not.<sup>74</sup> Moreover, anxiety, identified as the strongest predictor of poor sleep quality,<sup>77</sup> coexists with depressed mood and vasomotor symptoms in midlife women.<sup>78</sup> Depressed mood, anxiety, vasomotor symptoms, and sleep disturbances across the menopause transition appear to involve complex and bidirectional interrelationships.

In a subsample (n=526) from the Korean Genome and Epidemiology Study, regression analysis demonstrated that women going through surgical menopause were 2.1 (95% CI 1.055–4.303) times more likely to have insomnia compared with those experiencing natural menopause ( $P=.027$ ). Furthermore, women in the surgical menopause group who displayed more sleep-interfering behaviors also had a higher severity of insomnia symptoms compared with women experiencing natural menopause ( $\beta=0.26$ ,  $P=.03$ ).<sup>8</sup>

## SEXUAL DYSFUNCTION

Sexual dysfunction is one of the most prevalent and distressing consequences of early menopause. Although studies consistently demonstrate high rates of dysfunction compared with premenopausal women, prevalence rates vary by study, specific sexual disorder, and measures, ranging from 25% to 62%.<sup>79,80</sup> Unfortunately, the majority of women undergoing BSO for benign disease or risk-reducing BSO do not receive necessary information before surgery, support, or treatment for sexual consequences.<sup>81</sup>

Sexual dysfunctions related to menopause are primarily the result of decreased sex hormones, particularly estrogens and androgens. Estrogen mediates peripheral arousal, including vaginal congestion and lubrication. Androgens, more specifically testosterone, promote desire centrally through effects on neurotransmitters such as dopamine but also contribute to peripheral response. Androgen levels do not change significantly with the menopausal transition but decline gradually with age, such that testosterone levels in women in their late 40s or early 50s are approximately half of what they were in their early 20s.<sup>82</sup> After surgical menopause, androgen levels abruptly decline and are approximately one third of the level of a woman experiencing natural menopause, resulting in more severe sexual dysfunction.<sup>83</sup> The two most prevalent sexual disorders in all postmenopausal women, including those with early



menopause, are genitourinary syndrome of menopause and hypoactive sexual desire disorder.

Genitourinary syndrome of menopause is a constellation of physical changes and symptoms associated with estrogen deficiency, including vulvovaginal dryness, burning or irritation, dyspareunia and urinary symptoms of urgency, dysuria, and recurrent urinary tract infection.<sup>84</sup> At least 50% of postmenopausal women develop genitourinary syndrome of menopause and associated dyspareunia after menopause.<sup>85–87</sup> Unlike vasomotor symptoms, this is a chronic progressive condition that worsens from time of menopause. The development of genitourinary syndrome of menopause can have profoundly negative effects on a woman's quality of life, partner relationship, and self-esteem<sup>85</sup> and is associated with decreased frequency of sex, low libido, vaginal dryness, and anorgasmia.<sup>88</sup> Many women avoid intimacy because of vaginal discomfort.<sup>89</sup>

Women with surgical menopause present with a more severe genitourinary syndrome of menopause symptom profile than women with natural menopause, likely due the abrupt and persistent additional 50% decline in circulating androgen levels.<sup>90,91</sup> Several studies suggest that early menopause due to primary ovarian insufficiency is associated with more severe sexual dysfunction, including decreased sexual fantasies, decreased masturbation, reduced lubrication, and increased genital pain compared with age-matched women with natural menopause.<sup>92–94</sup> Not surprisingly, early menopause, either due to primary ovarian insufficiency or surgical menopause, can cause significant negative body image and self-esteem and sexual dysfunction. The younger the onset, the more likely the sexual problems.<sup>95</sup> In a cross-sectional study of 58 women with primary ovarian insufficiency (51 women were on HT) and a control group of 58 age-matched women with normal ovarian function, 62.1% of women with primary ovarian insufficiency compared with 37.8% of those in the control group reported sexual dysfunction as measured by a score of less than 26.5 on the Female Sexual Function Index.<sup>96</sup> There was no significant difference in the Female Sexual Function Index desire domain, but this domain was lowest in both groups.<sup>93</sup> Van der Stege et al found that women with primary ovarian insufficiency (n=81), compared with healthy women in a control group, reported more symptoms of decreased lubrication and increased genital pain but no differences in desire.<sup>97</sup>

Hypoactive sexual desire disorder is defined as persistent deficiency or absence of sexual thoughts, fantasies, desire for sexual activity, or all of these

associated with distress. It is highly prevalent in women of all ages (9.5%) and highest in women between the ages of 45 and 64 years (12.3%).<sup>98</sup> Women with surgical menopause have higher rates of hypoactive sexual desire disorder than women with natural menopause.<sup>99,100</sup> A prospective study of the psychological and sexual health and quality of life of 1,100 women aged 35–49 years who had undergone hysterectomy for benign disease with neither, one, or both ovaries removed found that women who had undergone BSO had significantly poorer outcomes at 24 months postsurgery. However, preoperative sexual concerns, including dyspareunia, vaginal dryness, low desire, and anorgasmia, were the best predictors of postoperative sexual dysfunction.<sup>101</sup>

The Women's International Study of Health and Sexuality survey<sup>80</sup> evaluated rates of hypoactive sexual desire disorder in three groups of women in menopause (surgical menopause age 20–49 years, surgical menopause age 50–70 years, and natural menopause) and compared them with rates of hypoactive sexual desire disorder in premenopausal women. Of the 2,050 patients, 26% of younger women in surgical menopause reported significantly higher distressing low desire compared with 14% of premenopausal women, 14% of older women in surgical menopause, and 9% of women in natural menopause. A similar survey of 1,345 European women aged 20–70 years<sup>102</sup> found that women who had undergone BSO were twice as likely to meet the criteria for hypoactive sexual desire disorder compared with premenopausal women or women in natural menopause. In contrast, a prospective study of sexual function in 323 perimenopausal women aged 45–55 years after either TAH or TAH–BSO found no difference in sexual function between groups at 1 year.<sup>103</sup>

## IDENTIFICATION OF WOMEN WITH *BRCA* MUTATIONS AND ASSOCIATED RISK

Many women with genetic mutations associated with breast and ovarian cancer remain unidentified despite increased public awareness of mutations and widespread availability of genetic testing. Clinicians should screen for and identify women who carry mutations that include *BRCA1* and *BRCA2*, because these women have a markedly increased risk of and early onset of breast and ovarian cancer<sup>104</sup> and should be informed of risk-reducing options.

The prevalence of *BRCA* mutations ranges between 0.2% and 0.3% in the general population. In women with breast cancer, the prevalence is approximately 3%, increasing to 6% in those with breast cancer before age 40 years, and can reach



20% in those with a positive family history.<sup>105</sup> The prevalence of *BRCA* mutations in the Ashkenazi Jewish population approaches 1 in 400, whereas the prevalence in the African American population is very low.<sup>106</sup> *BRCA* mutations account for 15% of women with ovarian cancer.<sup>107</sup>

The U.S. Preventive Services Task Force guidelines, updated in 2019, recommend that women's health clinicians screen all women for inherited risk of breast cancer. The U.S. Preventive Services Task Force recommends against routine genetic counseling and testing for individuals without a family history.<sup>108</sup> The National Comprehensive Center Network guidelines, updated in January 2019, offer specific criteria for hereditary cancer risk evaluation and possible testing, including female breast cancer diagnosed at 50 years of age or younger, triple-negative breast cancer diagnosed at 60 years of age or younger, and other criteria (see the National Comprehensive Center Network guidelines).<sup>109</sup> Screening all women for *BRCA* mutations is controversial. In a recent review, Lippi et al argue that women at low risk without a family history should be allowed to make an autonomous decision through shared decision making.<sup>110</sup>

### RISK-REDUCING OPTIONS INCLUDING SALPINGO-OOPHORECTOMY FOR WOMEN WITH *BRCA* MUTATIONS

Risk-reducing strategies including prophylactic bilateral mastectomy and BSO are indicated for women with *BRCA* mutations and are recommended for both ovarian and breast cancer risk reduction. Increased awareness of surgical options to reduce risk has led to an increase in risk-reducing BSO of 75% among women with *BRCA* mutations.<sup>111,112</sup> *BRCA*-affected women must consider the clinical evidence for the effectiveness of cancer risk reduction with risk-reducing BSO in balance with the significant short-term and long-term health consequences of early menopause.

The risk of developing breast cancer in women with *BRCA* 1 mutations by age 70 years is 72%, and the risk of ovarian cancer is 44%. In women with *BRCA* 2 mutations, the risk of breast cancer by age 70 years is 69%; for ovarian cancer it is 17%.<sup>113,114</sup> Mortality is significantly reduced in women with mutations who undergo risk-reducing BSO at the recommended age.<sup>115</sup> Current guidelines for women with *BRCA* 1 mutations are for risk-reducing BSO when childbearing is complete, between the ages of 35 and 40 years. Cancer onset in women with *BRCA* 2 mutations is 8–10 years later than in those with *BRCA* 1 mutations, with a recommendation for risk-reducing

BSO at 40–45 years of age.<sup>116–118</sup> Even when women with *BRCA* 1 mutations undergo risk-reducing BSO between the ages of 35 and 40 years, 4% have ovarian cancer diagnosed at the time of surgery. The risk increases substantially to 14.2% if women defer BSO until age 50 years. Risk-reducing BSO reduces the risk of ovarian cancer by 72–80% and breast cancer by 46–48%. Mortality is also reduced, predominantly as a result of a reduction in ovarian cancer-related mortality.

Although risk-reducing BSO substantially reduces cancer risk, early menopause is associated with significant short-term and long-term morbidity. Recent research efforts have identified less morbid and more acceptable alternatives, including oral contraceptives (OCs) and prophylactic bilateral salpingectomy with delayed oophorectomy. Oral contraceptives may be an initial or alternative ovarian cancer risk-reduction option for women before risk-reducing BSO or for women who choose not to undergo risk-reducing BSO. Oral contraceptive use in the general population is associated with a 20% reduction in ovarian cancer risk<sup>119</sup> and a slight increased risk of breast cancer with current use that declines progressively after discontinuation.<sup>120,121</sup>

The effect of OCs on breast and ovarian cancer risk in women with *BRCA* mutations before prophylactic BSO was clarified in a meta-analysis of 18 studies of women with *BRCA* mutations. Oral contraceptive use was associated with a significant reduction (SRR 0.50, 95% CI 0.33–0.75) in ovarian cancer. The reduction in risk with OC use in women with *BRCA* mutations is substantially higher than the 20% reduction observed in the general population.<sup>122</sup> No association was found between OC use and breast cancer in women with *BRCA* mutations (SRR 1.13, 95% CI 0.88–1.45).<sup>123</sup> Oral contraceptive use in women with *BRCA* mutations should be encouraged before risk-reducing BSO but is considered an inferior although reasonable option for risk reduction in women who decline risk-reducing BSO.

Evidence suggests that many ovarian cancers originate in the fallopian tubes and not the ovary. In the general population, opportunistic salpingectomy at the time of pelvic surgery for benign conditions reduces the incidence of ovarian cancer by 29–64% and has no significant effect on ovarian function.<sup>124,125</sup> The American College of Obstetricians and Gynecologists recommends opportunistic salpingectomy for average-risk women at the time of pelvic surgery for benign disease to reduce ovarian cancer risk. In young women with *BRCA* mutations, bilateral salpingectomy with delayed oophorectomy has been



considered as an alternative risk-reducing strategy for those hoping to preserve fertility and to prevent the excess morbidity of early menopause associated with risk-reducing BSO.<sup>126,127</sup> Data are lacking about whether bilateral salpingectomy with delayed oophorectomy is an effective strategy in women with *BRCA* mutations. The risk reduction seen with salpingectomy in women at average risk without a pathologic mutation is substantially lower than the risk reduction of risk-reducing BSO and is unacceptably high for women at elevated risk. In women with *BRCA* mutations at increased risk, the magnitude of ovarian cancer risk reduction and breast cancer risk reduction with salpingectomy is unknown. A 2017 review<sup>128</sup> concluded that further studies are needed before bilateral salpingectomy with delayed oophorectomy can be offered as a clinically effective, reasonable alternative to risk-reducing BSO in women with *BRCA* mutations.

## MANAGEMENT OF HEALTHY WOMEN WITH EARLY MENOPAUSE

Hormone therapy in women with early menopause due to primary ovarian insufficiency or BSO is standard of care until the average age of natural menopause (51 years), in contrast to women aged older than 50 years, for whom menopausal HT is indicated for symptom management and not disease prevention. Unfortunately, the Women's Health Initiative has had a profound and lasting effect on the use of HT, even in young women younger than 50 years of age after TAH-BSO for benign disease. The use of HT has decreased dramatically since the publication of the Women's Health Initiative,<sup>129</sup> with only 5–6% of women with early menopause currently using HT.<sup>130</sup>

Clinicians must understand that the Women's Health Initiative findings do not apply to women experiencing early menopause. Hormone therapy use in women with early menopause is unacceptably low, despite guidelines from national and international organizations, including the North American Menopause Society, the American Society for Reproductive Medicine, the International Menopause Society, the British Menopause Society, and the American College of Obstetricians and Gynecologists, recommending that those with early menopause (natural, induced, or surgical) be considered for HT until the average age of menopause to prevent the health consequences of loss of ovarian hormones.<sup>131–134</sup> A recent review of clinical practice management of early menopause or primary ovarian insufficiency found consistency in support for HT until the average age

**Table 1. Observed Risks Associated With Loss of Ovarian Function At Younger Than 45 Years of Age**

Risks	Estrogen Therapy Effects	Reference(s)
Neurologic functions		
Dementia	Yes	56,61
Neuritic plaques	Yes	63
Global cognition	Yes	53,60
Parkinsonism	No	62
Depression	Yes	69
Anxiety	No	77
Genitourinary	Yes	136
menopausal symptoms		
Hypoactive sexual desire disorder		136,138
Bone metabolism		
Bone loss (2.4%/y)	Yes	46
Fracture risk	Yes	47
Cardiovascular effects		
Risk of angina	Yes	40
Impaired endothelial function	Yes	31
Heart failure	Yes	34
Ischemic stroke	Yes	35,38

of menopause<sup>135</sup> to mitigate the negative and cumulative health consequences of early menopause.

Hormone therapy until age 50 has been shown to mitigate some but not all of the health consequences of early menopause (Table 1). Hormone therapy is the mainstay and most effective treatment for menopause symptoms and improves quality of life. Numerous clinical trials have shown the effectiveness of HT to prevent osteoporosis and reduce the risk of fractures. Hormone therapy in young women reduces CVD risk and mortality and offsets the cognitive effect of early estrogen deficiency.<sup>131,136</sup> HT benefits sexual health, mitigating the development of genitourinary syndrome of menopause and dyspareunia. Hormone therapy alone may be helpful but is often inadequate for treatment of hypoactive sexual desire disorder, anxiety, and depression in early menopause.

Appropriate treatment options for women with early menopause include OCs and HT (the optimal estrogen dose has not been studied; however, higher doses are often required for symptom management in younger women). Studies on HT in hypogonadal girls with Turner syndrome suggest that transdermal E2 with serum E2 levels in the reproductive-age range are most physiologic.<sup>137</sup> Transdermal E2 (0.05–0.1 mg/d), oral E2 (1–2 mg), or conjugated equine estrogens (0.625–1.25



**Table 2. Current Estrogen Preparation Doses and Routes of Administration**

Product	Available Doses
Oral	
Synthetic conjugated estrogens (Cenestin)	0.3 mg, 0.625 mg, 1.25 mg
Equine conjugated estrogens (Premarin)	0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, 1.25 mg, 2.5 mg
Micronized estradiol (Estrace, Gynodiol)	0.5 mg, 1.0 mg, 2 mg
Esterified estrogens (Menest)	0.3 mg, 0.625 mg, 1.25 mg, 2.5 mg
Estropipate (Ogen, Ortho-Est)	0.625 mg, 1.25 mg, 2.5 mg
Transdermal systems	
17-beta estradiol (Estraderm, Vivelle, Alora, Climara, Esclim, Menostar)	0.025 mg, 0.0375 mg, 0.05 mg, 0.075 mg–0.1 mg/d, 14 micrograms/d
17-beta estradiol + norethindrone acetate or levonorgestrel (Combipatch, Climara Pro)	0.045–0.05 mg/d + 0.14, 0.15, 0.25 mg/d
Topical	
17-beta estradiol	
Estrasorb	3.48 g/d delivers 0.05 mg/estradiol/d
EstroGel	1.25 g/d delivers 0.075 mg/estradiol/d
Injectable	
Estradiol valerate in oil (Delestrogen)	10 mg/mL–40 mg/mL
Estradiol cypionate in oil (Depo-Estradiol)	5 mg/mL
Vaginal	
Tablets (Vagifem, Yuvaferm)	10-microgram estradiol/tablet
Vaginal insert (Imvexxy)	4/10 micrograms estradiol
Creams	
Estrace	0.1 mg estradiol/g
Premarin	0.625 conjugated equine estrogen mg/g
Ogen	1.5 mg estropipate/g
Rings	
Estring	Estradiol 2 mg/3 months/ring (7.5 micrograms/d)
Femring	Estradiol 0.05 mg–1 mg/d for 90 days (systemic absorption)

mg) are usually effective for symptom relief and appropriate doses for long-term management (Table 2). For women without a uterus, estrogen alone is appropriate. For women with a uterus, estrogen in combination with an oral daily progestogen or cyclic progestogen such as medroxyprogesterone acetate 5–10 mg/d × 12 days or micronized progesterone 200 mg/d × 12 days is required for endometrial protection. Women should be told to expect symptom relief within 6–8 weeks.

Sexual dysfunction in women is complex and should be considered in a biopsychosocial context. Office-based counseling or referral to psychotherapy is recommended, especially for women with early menopause or primary ovarian insufficiency to address the negative psychological effect of the medical consequences of early menopause, including infertility.

Hormone therapy alone may be inadequate to treat sexual dysfunction in postmenopausal women. For those with GSM not responding to HT, treatments include local HT including estrogen creams, ring, pill and insert, DHEA (prasterone), and an oral SERM (ospemifene). Fractional CO<sub>2</sub> or Holmium laser energies may hold promise but need larger controlled trials.<sup>138</sup> For those not responding to

HT, data support androgen therapy in addition to HT for postmenopausal women with hypoactive sexual desire disorder. The Endocrine Society recommends a 3–6-month trial of androgen therapy to treat hypoactive sexual desire disorder in postmenopausal women.<sup>139</sup> A recent systematic review and meta-analysis of randomized controlled trial data on testosterone in women confirmed efficacy in postmenopausal women with hypoactive sexual desire disorder. Transdermal preparations are preferred to reduce liver effects. Small studies of androgen therapy do not support benefit on well-being or musculoskeletal and cognitive health.<sup>140</sup> A recent consensus recommendation published by a multidisciplinary task force of clinicians from leading societies, including the International Menopause Society, the Endocrine Society, the European Menopause and Andropause Society, the International Society for Sexual Medicine, the International Society for the Study of Women's Sexual Health, the North American Menopause Society, the Federacion Latinoamericana de Sociedades de Climaterio y Menopausia, the Royal College of Obstetricians and Gynaecologists, the International Society of Endocrinology, the Endocrine Society of Australia, and the Royal Australian



and New Zealand College of Obstetricians and Gynaecologists,<sup>141</sup> reviewed the safety and efficacy of testosterone in menopausal women and concluded that data support the use of physiologic testosterone for postmenopausal women with hypoactive sexual desire disorder.

Currently, there are no U.S. Food and Drug Administration–approved testosterone therapies available for women. Earlier studies of a 300-microgram/d transdermal testosterone patch demonstrated efficacy in menopausal women with hypoactive sexual desire disorder, but it was not approved by the FDA owing to lack of long-term safety data. Data from those studies demonstrate that a 300-microgram/d testosterone patch results in physiologic serum testosterone levels of less than 70 ng/dL.<sup>142</sup> Without an FDA-approved option, clinicians are forced to use compounded testosterone or topical male products dosed for women. Typically, topical male testosterone gel (1%) is dosed at 2.5 mg of gel/day, or 1/10th of the 25-mg gel daily topical dose for men. Alternatively compounded testosterone cream (1% or 2%) can be formulated to deliver a typical dose of 250 micrograms/d of testosterone). Clinicians should confirm that serum testosterone levels remain in the female physiologic range. Clearly, an FDA-approved testosterone product for women is needed.

Flibanserin, a nonhormonal, centrally acting, daily, oral multifunctional serotonin agonist and antagonist<sup>143</sup> is approved for the treatment of premenopausal women with acquired hypoactive sexual desire disorder. However, clinical trials in postmenopausal women demonstrated similar efficacy and safety as found in premenopausal women.<sup>144,145</sup> Bremelanotide is also approved for the treatment of premenopausal women with acquired hypoactive sexual desire disorder. It is a cyclic 7-amino-acid melanocortin-receptor agonist that is self-administered using a subcutaneous autoinjector 45 minutes before anticipated sexual activity, with duration of action to 16 hours.<sup>146</sup> Both flibanserin and bremelanotide are nonhormonal therapies and may be reasonable therapeutic options for women with early menopause and hypoactive sexual desire disorder.

Mood disorders are common in the menopausal transition and early postmenopause. Anxiety and depression, much like sexual dysfunction, are often inadequately treated with HT alone. There is some evidence that estrogen has antidepressant effects similar in magnitude to common antidepressant options in perimenopausal women—but not postmenopausal women—suggesting a “window of opportunity” for effective use of estrogen therapy.<sup>67</sup> Maki et al<sup>67</sup> note that estrogen may augment a clinical response to an antidepressant in perimenopausal and postmenopausal women but remind clinicians that it

is not FDA-approved for that indication. Therefore, in women with early menopause–associated anxiety or depression, first-line treatment should be proven therapeutic options including antidepressants and psychotherapy. Treating sleep disturbance should also be considered as part of treatment for depression.<sup>67</sup>

## MANAGEMENT OF EARLY MENOPAUSE IN WOMEN WITH *BRCA* MUTATIONS AFTER RISK-REDUCING BILATERAL SALPINGO-OOPHORECTOMY

Risk-reducing BSO in young women with *BRCA* mutations is recommended, although the consequences of early menopause in these women, often in their 30s, are substantial and management remains challenging. There are no randomized trials or high-quality data for HT in women with *BRCA* mutations without a cancer diagnosis who have undergone risk-reducing BSO to inform clinicians. Without randomized controlled trial data, many clinicians remain fearful of HT in these women, despite the known consequences of early menopause. Women undergoing risk-reducing BSO are also fearful of the unknown effects of HT on their cancer risk given the extensive negative publicity about HT. Nonhormonal approaches in women with risk-reducing BSO do not address the significant consequences of early menopause.

Several observational studies of HT in women with *BRCA* mutations after risk-reducing BSO are available.<sup>147,148</sup> These studies are limited by their short-term, observational design and are confounded by heterogeneous characteristics of women with *BRCA* mutations undergoing risk-reducing BSO. Women with *BRCA1* and *BRCA2* mutations have different risk of breast and ovarian cancer at baseline. In addition, breast cancers in women with *BRCA1* mutations are usually hormone receptor–negative, whereas those in women with *BRCA2* mutations are generally estrogen and progesterone receptor–positive,<sup>149</sup> making it plausible that HT to manage early menopause might affect future risk differently. Other factors, such as TAH at the time of risk-reducing BSO or prophylactic mastectomy at the time of risk-reducing BSO, might influence subsequent risk of cancer with HT.

Importantly, all observational studies on HT in risk-reducing BSO are consistent and<sup>147</sup> suggest that HT in this population does not increase breast or ovarian cancer risk, even in women who have intact breasts. Randomized controlled trials of HT in women with *BRCA* mutations undergoing risk-reducing BSO are unlikely to be conducted. A study of 155 women with *BRCA1* or *BRCA2* mutations undergoing risk-reducing BSO (60% using HT) found



that, after a mean of 3.6 years, risk-reducing BSO was associated with a 60% reduction in breast cancer ( $P < .05$ ) regardless of whether they used estrogen-only therapy or estrogen-progestogen therapy.<sup>146</sup> Armstrong et al<sup>150</sup> found that HT use after risk-reducing BSO until age 50 years led to a gain in life expectancy.

A retrospective study of HT use in women with *BRCA1* mutations with and without breast cancer after natural menopause or risk-reducing BSO found the adjusted odds ratio for women who used HT was not significant (odds ratio 0.80, 95% CI 0.55–1.16).<sup>151</sup> A prospective longitudinal cohort study of 872 women who underwent risk-reducing BSO found ever use of HT (373 women) was not associated with an increase in risk of breast cancer (HR 0.97, 95% CI 0.62–1.52).<sup>152</sup> A 2016 review,<sup>153</sup> a 2018 systematic literature review,<sup>154</sup> and a 2019 review<sup>155</sup> all conclude that HT may offer benefit to women with *BRCA* mutations with early menopause after risk-reducing BSO, does not affect breast cancer risk, and is reasonable at least until age 50 years.

Long-term, statistically powered studies are needed to provide definitive conclusions about formulation of HT and optimal duration of use. Based on limited observational data, HT should be considered for all women with *BRCA* mutations undergoing risk-reducing BSO until the age of natural menopause. In this population, education is critical for women before risk-reducing BSO regarding the consequences of early menopause, the data supporting the benefit of HT, and the absence of data supporting an increased breast cancer risk in a model of shared decision making.

## CONCLUSION

Early menopause, BSO before age 51 years, risk-reducing BSO, and primary ovarian insufficiency regardless of the underlying clinical condition or etiology have similar downstream effects on vasomotor symptoms, neurologic function, cardiovascular risk, bone and soft tissue changes, mood disturbances, sexual dysfunction, and depression. Clinicians must be aware of these consequences—some of which are clinically silent for many years. In particular, vasomotor symptoms, sleep, anxiety, depression, and sexual dysfunction are more prevalent in this group of women and greatly affect their quality of life. The Women's Health Initiative concerns regarding the use of HT in menopausal women should not be applied to women with early menopause. We have highlighted the positive effect of appropriate HT and adjunctive and alternative therapies for management of these conditions, including in women with

*BRCA* mutations. Hormone therapy can mitigate many of these conditions (Table 1) and improve the quality of life in women with early menopause.

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