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Natural Support for Premenopause and Beyond

BY JOSEPH L. MAYO, MD, FACOG

ABSTRACT: *More than one-third of women in the United States are experiencing or have been through menopause. A gradual process, natural menopause occurs in most women by ages 50 to 51. Some women may begin to notice the beginning stages of hormonal changes as early as age 35 to 40, a period known as late premenopause. From premenopause and beyond, women may be challenged with managing a barrage of symptoms, both physiological and psychological, as well as the increased risk of age-related disease, particularly heart disease and osteoporosis. Many women are seeking natural support for hormone-related symptoms and associated risk factors, particularly because of the well-known risks associated with hormone replacement therapy. Natural treatment strategies should focus on both symptom relief and disease prevention, and may include nutritional supplements, herbs, and healthy dietary and lifestyle choices.*

As a woman's reproductive years come to an end, she begins to experience the first signs of menopause. Menopause is the proper term used after menstruation has ceased for one year, after which women are considered postmenopausal. Unless brought about by surgery, chemotherapy, or other artificial factors, natural menopause occurs in most women by age 50 to 51. Perimenopause is the time leading up to menopause, which usually begins several years before, often between the ages of 40 and 51.[1] During this time, the body is adjusting to erratic hormone levels, which become evident by the start of irregular menstrual bleeding (shortened or lengthened cycles and diminished menstrual flow) and hot flushes. Between the ages of 35 to 40, as hormonal changes begin to occur, some women experience noticeable menstrual cycle changes and, if at all, occasional hot flushes. Other physical and emotional symptoms may start to be apparent during this period known as late premenopause.[2]

More than one-third of women in the United States—over 39 million—are experiencing or have been through menopause, many of whom have endured symptoms of hormonal changes.[3] Changing hormone levels often cause vasomotor symptoms as experienced by hot flushes or night sweats, which are the most predominant symptoms estimated to occur in 6% to 63% of premenopausal women; 28% to 65% of perimenopausal women; and 93% of women in their first two postmenopausal years.[1] Although the pattern and intensity of symptoms may vary greatly, many women also experience irregular bleeding; decreased vaginal lubrication; or thinning vaginal mucosa. Other symptoms may include mood swings, sleep disturbances, depression, urinary problems and incontinence, vaginal irritation, and painful intercourse (Table 1).

Table 1. Signs and symptoms of hormonal changes.

- Hot flushes/night sweats
- Irregular or dysfunctional uterine bleeding (e.g., more or less frequent, lighter or heavier, shorter or longer in duration, random spotting)
- Decreased vaginal lubrication and a thinning vaginal mucosa, both of which may cause painful intercourse
- Depression and mood swings
- Memory loss and impaired cognitive function
- Sleep disturbances
- Cold hands and feet
- Weight gain
- Urinary incontinence
- Loss of libido (due to declining testosterone)
- Headaches

Transitional Hormone Changes

As menopause approaches, ovarian function gradually declines. While the ovaries continue to secrete estrogen, progesterone, and androgen, hormonal changes gradually occur in the relationship (or ratio) of one hormone to another. Follicle-stimulating hormone (FSH), which stimulates the development of estrogen, increases at a rate greater than luteinizing hormone (LH), which is closely associated with progesterone production. Triggered by changing FSH and LH levels, estrogen production tends to rise with age until menopause approaches, and progesterone production gradually decreases, resulting in excess or unopposed estrogen. This "hyperestrogenic state" is common in premenopausal and perimenopausal women. During the last year of perimenopause, estrogen levels decrease very rapidly. The decline in ovarian estrogen and progesterone production and rising follicle-stimulating hormone and luteinizing hormone levels prompts the onset of menopause.[1,4]

Once a woman reaches menopause, the adrenal glands and fat cells become the primary sources of estrogen production. The adrenal glands produce androstenedione—an androgen that is converted to estrogen via the aromatase enzyme in peripheral skin, adipose, and muscle tissue.[5] Because adipose tissue is a primary location for androgen conversion to estrogen, relatively lean women tend to experience menopause earlier than heavier women.

Adrenopause in Women

The adrenal glands not only support androgen/estrogen metabolism, they also support the body's "adaptogenic" response. Adaptogenic refers to the body's ability to cope with, or adapt to, stress. While it is normal for women to be under constant stress in today's society, chronic stress may contribute to some degree of adrenal fatigue—possibly predisposing a woman to health problems long before she even reaches menopause. Indeed, excessive or prolonged activation of the stress hormones increases the risk of heart disease, high blood pressure, obesity, peptic ulcers, and asthma. Additionally, dehydroepiandrosterone (DHEA) levels have been shown to fall dramatically during times of extreme stress—presumably through the increased production of cortisol.

Circulating testosterone concentrations have been reported to fall by approximately 50% between the ages of 20 and 40 and continue to decline with age, particularly during the decade following menopause.[6,7] The decline in circulating testosterone, known as adrenopause, is influenced by a shift in precursor steroids, and is largely responsible for

diminished sexual function, including loss of libido and loss of sexual response in postmenopausal women. This testosterone level reduction may also decrease energy levels and sense of well-being.[6]

The majority of a postmenopausal woman's circulating testosterone is dependent upon adrenal androstenedione synthesis, with the remaining produced by circulating androstenedione or intracellularly from DHEA. The synthesis of adrenal androgens begins with the conversion of cholesterol to pregnenelone. Pregnenelone is then converted to either cortisol—the stress hormone—or DHEA. DHEA is subsequently converted to androstenedione, which then produces either testosterone or estrogen (Figure 1).

Estrogen Metabolism and the Liver

There are three main types of estrogen found in significant levels in human plasma, namely estradiol, estrone, and estriol. Estradiol is the principle estrogen secreted in the body, whereas estrone is secreted in only small amounts; these two estrogens can be converted back and forth or into the less potent estrogen, estriol. Estradiol and estrone are metabolized primarily in the liver. In this process, different cytochrome p450 enzymes add a hydroxl group (-OH) to either the 2 position, 4 position, or 16 position of the main estrogen structure. This process is known as hydroxylation and can occur on estrone or estradiol. The resulting metabolites of the 2- and 4- hydroxylations can then be methylated, changing their biological activity, or else they are conjugated with either glucuronic acid or sulfate, forming conjugates that are water soluble and excretable in the urine.

It is important to note that all estrogen metabolites circulate for a time and have varying degrees of activity in the body. The relative degrees of 2-, 4-, and 16α-hydroxylation influence estrogenic activity, and may play a significant role in various diseases. For instance, the 2-hydroxylation of estradiol and estrone produces the weaker estrogen metabolite 2-hydroxyestrone, or "good" estrogen, which is thought to beneficially impact hormone balance and health of breast cells. In contrast, the 16α- and 4-hydroxylation produce more potent compounds with persistent estrogenic activity, and are thought to be related to a variety of conditions related to estrogen dominance or imbalance. The 4-hydroxylated estrogens can be converted to another metabolite, a 4 catechol estrogen, that is similar to a free radical and can alter DNA and proteins. The 16α- and 4-hydroxylated metabolites are thought to be involved in an increased risk of breast cancer, abnormal endometrial hyperplasia, and a host of other health concerns.

If liver function is diminished, the activity of more potent estrogen metabolites may be increased. It is therefore vital for women to maintain healthy liver function, particularly from premenopause and beyond. Certain phytonutrients combined with a healthy diet and lifestyle can support liver health and normal estrogen metabolism. (For a detailed discussion on estrogen metabolism, please refer to the Applied Nutritional Science Report entitled, *Nutritional Influences on Estrogen Metabolism*, by Douglas C. Hall, MD)

CHANGING HORMONE LEVELS: WHAT THIS MEANS TO WOMEN'S HEALTH

Depending on the health of the woman, the changes in hormone levels that occur during menopause may not only cause undesirable symptoms, they may also contribute to disease risk and functional abnormalities. This is especially the case in women who are already at an increased risk because of genetics, illness, or poor dietary and lifestyle choices.

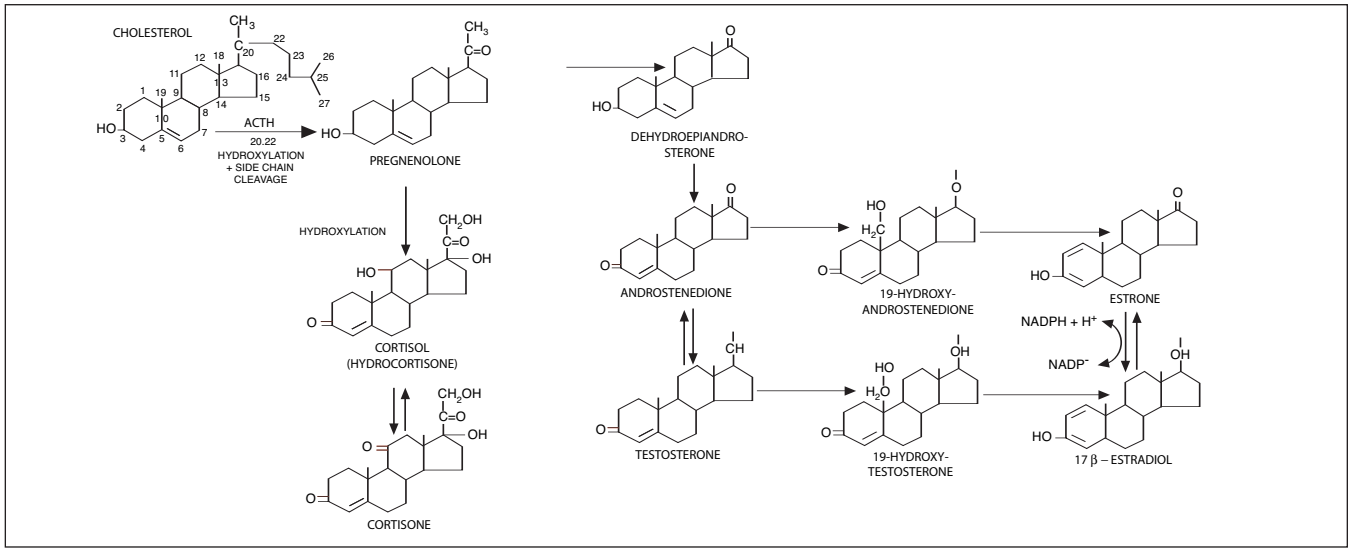
Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding (DUB) is a functional abnormality that commonly occurs during perimenopause, with greater than 50% of cases in women over age 40.[8,9] Normal endometrial bleeding (menstruation) occurs as a result of stimulation of the endometrium by the physiologic levels and balance of estrogen and progesterone present in the normal ovulatory cycle, and by the subsequent rapid withdrawal of these two hormones. This withdrawal results in complete and rapid shedding of the entire functional layer of the endometrium. A change in the balanced estrogen-progesterone relationship during perimenopause can result in four clinical etiologies of true DUB.[9,10]

Nonovulatory DUB—Greater than 70% of DUB cases are associated with anovulation. The bleeding in anovulatory women is generally the result of continued stimulation of the endometrium with unopposed estrogen, which occurs when there is a dysfunction of the hypothalamic-pituitary-ovarian axis. The endometrium, thickened by the estrogen, then sloughs incompletely and irregularly, and bleeding becomes irregular, prolonged, and/or profuse. The absence of progesterone results in deficient endometrial prostaglandins so that appropriate spasm of the coild arterioles of the endometrium is lacking. This also results in irregular and incomplete shedding of the endometrium.

Irregular Ripening of the Endometrium (Luteal Phase Defect)—This occurs in ovulatory cycles where the corpus luteum production of progesterone is inadequate to permit development of a receptive endometrium. Any disturbance of follicular growth and development can produce an inadequate follicle and a deficient corpus luteum. Patients with luteal phase

Figure 1. Biosynthesis of Androgens, Estrogens, and Cortisone



defects can present primarily with DUB manifested as premenstrual bleeding, menorrhagia, or polymenorrhea.

Endometrial Atrophy (or Threshold Bleeding)—The normal amount of estrogen secreted during the proliferative phase of the cycle results in a stable endometrium that is intact and does not bleed. In the absence of estrogen, or with the minimal levels present premenarchally or postmenopausally, the endometrium is so unstimulated and atrophic that no bleeding occurs. However, with persistent intermediate levels of estrogen, irregular bleeding occurs. This is because there is enough estrogen to stimulate the endometrium but not enough to stabilize it, keep it intact, and maintain it.

Note: The types of uterine bleeding discussed are functional conditions. Uterine bleeding may also be associated with a serious health condition, such as vaginitis or cancer. Therefore, a thorough patient assessment by the healthcare provider is recommended.

Osteoporosis and Cardiovascular Disease

Among most prevalent diseases associated with postmenopausal women are osteoporosis and cardiovascular disease. Both of these diseases are strongly linked to hormonal levels, as well as to dietary and lifestyle habits. Table 2 lists some of the common risk factors associated with osteoporosis and cardiovascular disease.

Table 2. Risk Factors Associated with Osteoporosis and Cardiovascular Disease

Osteoporosis

- Reduced estrogen/progesterone as a result of menopause
- Decreased androgen as a result of aging
- Lack of exercise
- Smoking
- Heavy alcohol or caffeine consumption
- Reduced muscle mass
- Heredity
- Asian or European descent
- Use of certain drugs, including corticosteroids and anticonvulsants
- Inadequate calcium and vitamin D intake

Cardiovascular Disease

- Reduced estrogen as a result of menopause
- Smoking
- High blood pressure
- Elevated levels of plasma/serum cholesterol
- High LDL levels
- Low HDL levels
- Elevated plasma triglycerides
- Diabetes
- Obesity
- Truncal obesity (“apple-shape”)
- Stress
- Lack of exercise

The ovarian steroids estrogen, androgen, and progesterone play an important role in the regulation of bone remodeling (resorption/formation). Results of research conducted during the past 10 years shows that estrogen and androgen decrease the rate of bone resorption (i.e., the breakdown of bone) and stimulate bone formation.[11] Although its role is less well understood, progesterone has also been shown to beneficially influence bone remodeling, possibly due to its estrogenic and androgenic activities.[11] Thus, as hormone levels decline, the body’s ability to keep up with the natural process of bone remodeling also declines, contributing to brittle bones and an increased risk of fractures. (For a detailed discussion of osteoporosis and bone health, please refer to the Applied Nutritional Science Report entitled, *Nutritional Strategies in the Prevention of Osteoporosis*, by Neil Hirschenbein, MD, PhD, CCN.)

Previous research suggested that estrogen protected women from heart disease, presumably by promoting a favorable plasma lipid profile and healthy blood circulation.[12] A comparison of plasma lipid levels between 542 healthy, non-obese, pre- and postmenopausal women showed significant increases for postmenopausal women in total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels. Decreases in high-density lipoprotein (HDL) cholesterol levels were also reported. These results were observed after standardization for age, body mass index, and other confounding variables, and were thus accredited to menopause. While the changes in plasma lipids that occur during menopause are likely the result of many factors, estrogen may play both a direct and indirect role. Estrogen itself appears to lower LDL levels via up-regulation of apolipoprotein B100.[13] Furthermore, the reduced estrogen levels in postmenopausal women cause a relatively higher concentration of circulating testosterone. Elevated testosterone levels are known to increase LDL levels and decrease HDL levels by increasing hepatic lipase activity.[14] (For more information on maintaining cardiovascular health, please refer to the Applied Nutritional Science Report entitled, *Part II: Cardiovascular Disease, Nutritional Management of Clinical Markers,* by Decker Weiss, ND.)

While increasing estrogen levels during menopause—such as with hormone replacement therapy (HRT)—may seem like the logical solution to preventing these debilitating diseases, the effect of HRT on cardiovascular disease has recently been a subject of great controversy. In 2001, researchers found that women who took HRT tended to be more educated, in a higher income bracket, of lower weight and body mass index, healthier, and at lower risk for cardiovascular disease than those who were not on HRT. This was reflective of lifestyle, and not of HRT itself. Therefore, previous studies suggesting a lower risk of cardiovascular disease with HRT may have been due to the differences in the relative risks of the subject populations, and not to the HRT.[15]

The recent Women’s Health Initiative (WHI) study published in the *Journal of the American Medical Association* indicated that HRT does not provide effective prevention of cardiovascular disease and placed some women at a higher risk of cardiovascular disease.[16] The Heart and Estrogen/Progestin Replacement Study (HERS) also showed that HRT did not reduce the risk of CVD.[17] These findings were confirmed in a scientific review conducted for the U.S. Preventive Services Task Force and reported in 2002, wherein researchers identified increased risk of coronary disease, stroke, and thromboembolic events with 5 or more years of HRT use.[18] These findings led the Task Force to recommend against using HRT for the prevention of chronic conditions and emphasize the need to redirect attention to other methods of cardiovascular disease risk reduction in postmenopausal women.[19] In January 2003, the U.S. Food and Drug Administration outlined new labeling requirements for all HRT preparations, emphasizing that HRT increases the risk of heart disease, heart attack, and stroke.[20]

In addition to contributing to the onset of cardiovascular disease, HRT has been implicated as a possible cause of estrogen-related cancers (i.e., breast, ovarian, endometrial) and gallbladder disease.[21,22] With research demonstrating the negative effects of HRT, it may be difficult to determine what action to take to simultaneously relieve menopausal symptoms and reduce disease risk. Fortunately, there are several natural alternatives to maintaining a healthy hormonal balance and overall health throughout the transitional years.

NUTRITIONAL SUPPORT FOR HORMONAL BALANCE AND OVERALL HEALTH

Nutritional support for women during premenopause and throughout the postmenopausal years should include natural ways to support hormone balance and the adrenal gland's adaptogenic response, as well as ways to help reduce the risk of endometrial hyperplasia, osteoporosis, and cardiovascular disease. Along with a healthy diet and lifestyle, these goals can be accomplished through various nutritional and herbal supplements.

Soy Isoflavones

The potential health benefits of soybeans and soy foods have become increasingly recognized worldwide. This is due largely to the apparent health benefits imparted by the traditional Asian diet, which is very high in soy foods, as well as low in saturated fat, and high in dietary fiber.[23] Soybeans are legumes that are rich in phytoestrogens—plant compounds that are structurally similar to estrogen and possess weak estrogenic activity. Specific phytoestrogens known as isoflavones include genistin, daidzin, and glycitin, and are believed to provide many of the health benefits of the traditional Asian diet.[24] Isoflavones appear to exert a variety of effects that may protect against symptoms associated with menopause, as well as age-related diseases including osteoporosis and cardiovascular disease. For those patients who may be allergic to soy, isoflavones are also found in red clover (*Trifolium pretense*) and kudzu root (e.g., *Pueraria tuberose, Pueraria lobata*).

Menopause—Postmenopausal Japanese women who consume soy foods experience significantly reduced symptoms of menopause and are less likely to use hormone replacement therapy (HRT) compared to American women who do not include soy foods in their diet.[25] In one study, women who received 45 g/day of soy flour reportedly experienced a 40% reduction of hot flashes after a period of 6 weeks compared to women who received the same amount of wheat flour.[26] All of the women included in the study had not experienced a menstrual cycle for at least 12 months and were experiencing at least 14 hot flashes per week.

Osteoporosis—In a recent double-blind, randomized, controlled trial of postmenopausal women (aged 48 to 62 years) with initial low bone mass, soy isoflavones given at a dose of 80 mg per day had a significant effect on maintaining hip bone mineral content.[27] Additionally, Dalais et al. reported that 45 mg/day of soy isoflavones, consumed over two 12-week periods, increased bone density in 13 postmenopausal women.[28]

Cardiovascular Disease—In experimental models, soy consumption has been shown to reduce cardiovascular disease and prevent LDL cholesterol oxidation—one of the main causes of the progressive hardening and blocking of arteries. Sirtori et al. reported that the substitution of soy protein for animal protein in the diets of hypercholesterolemic humans led to a marked decrease in the concentration of serum total cholesterol, LDL cholesterol, and triglycerides without significantly affecting HDL cholesterol concentrations.[29] While soy consumption is known to reduce cholesterol in hypercholesterolemic subjects, a recent study showed that a high isoflavone diet consumed for 3 menstrual cycles (approximately 129 mg/day) lowered LDL cholesterol up to 10% and lowered the ratio of LDL to HDL cholesterol by 13.8% in premenopausal women with normal cholesterol levels.[30]

Supplemental DHEA

DHEA levels are at their highest during a person's twenties and then decrease dramatically over the next 5 to 6 decades. This decline has been associated with diminished sexual function, fatigue, and other age-related malfunctions. Research surrounding supplemental DHEA has focused on this age-related decline in androgen circulation and its impact on sexual function, energy, and general health.[31]

In a recent study of 105 women aged 24 to 78 years presenting with a 6-month period of decreased sexual desire, a strong correlation was found with androgen deficiency. In fact, decreased levels of DHEA-S and testosterone were found in 70% of subjects, and appeared to be caused by adrenal insufficiency rather than decreased ovarian function.[32]

In a randomized, double-blind study, supplemental DHEA was shown to have positive results in 16 postmenopausal women. In this study, a one time acute dose (300 mg) of DHEA increased concentrations of DHEA-S by 2-5-fold, and women reported significant increases in both mental and physical sexual arousal.[33]

Supplemental DHEA may be beneficial for women; however, more than 25 mg/day is associated with increased estradiol and testosterone production. High concentrations of estradiol may be a risk factor for breast or endometrial cancer in postmenopausal women. Additionally, excess testosterone can lead to masculinization (e.g., facial hair, deepened voice, feelings of hostility and aggression) and is associated with an increased risk of cardiovascular disease.[33]

Calcium and Other Bone-Supporting Nutrients

A substantial amount of evidence indicates that adequate calcium intake helps to prevent the excessive bone loss that is associated with osteoporosis. In a well-known study, Reid et al. reported a 43% reduction in bone loss in postmenopausal women who supplemented their regular diets with 1,000 mg/day of calcium for 2 years compared to postmenopausal women receiving a placebo.[34]

In addition to calcium, vitamin D is recognized as an important player in the maintenance of bone health throughout the menopausal years. Other nutrients such as magnesium, zinc, copper, and manganese are also important. Evidence further suggests that the trace mineral boron may help to maintain bone health by increasing circulating levels of estrogen.[35,36] In fact, boron supplementation (3 mg/day) was shown to significantly reduce urinary calcium loss and increase the concentrations of circulating estrogen in postmenopausal women who were previously placed on a low boron diet (0.25 mg/day).[37]

Vitamin E

Vitamin E is is best known for its antioxidant properties and ability to support cardiovascular health. As an antioxidant, vitamin E protects against lipid peroxidation of low-density lipoprotein (LDL), which can initiate a sequence of events leading to the presence of atherosclerotic plaque.[38] Vitamin E may also support healthy blood circulation since deficiency of vitamin E leads to increased thromboxane A2, which is known to stimulate platelet aggregation.[39] In addition to being cardioprotective, some studies have suggested that vitamin E inhibits the growth of breast cancer cells—possibly by inhibiting the expression of vascular endothelial growth factor—which encourages angiogenesis.[40]

Vitamin C

Vitamin C intake becomes especially important for women approaching menopause. The increased physical and emotional stress experienced by some women may increase the need for vitamin C, as stress has been shown to trigger the biosynthesis and secretion of adrenaline—and vitamin C is required for the synthesis of catecholamines.[39] Prolonged activation of the stress response can deplete tissues of vitamin C, which in turn can suppress the immune response. Additionally, vitamin C may help to reduce the risk of mortality from both heart disease and cancer.[39,41] In fact, numerous epidemiological studies suggest that a diet high in vitamin C may help protect against cardiovascular disease by acting as an antioxidant, supporting strong blood vessel structures by its role in collagen synthesis, and possibly improving blood lipid levels.[41] Vitamin C may help to protect against cancer through its involvement in carcinogen detoxification via antioxidant and free radical scavenging activity, and its role in enhancing immune response.[41]

Bioflavonoids

Bioflavonoids are bioactive compounds found throughout the plant kingdom. Thousands of different bioflavonoids have been identified and their biologic activity can vary greatly. Bioflavonoids, such as rutin, hesperidin, and quercetin, are well known for their antioxidant and anti-inflammatory properties and their ability to help maintain healthy capillary integrity. Additionally, certain bioflavonoids, such as quercetin, have been shown to bind to type II estrogen binding sites and as such, inhibit the growth of human ovarian cancer cell lines in vitro.[42-44] Rutin and its semi-synthetic form, hydroxyrutin, are known to contribute to cardiovascular health by supporting the peripheral vascular system and capillary integrity.

Pyridoxine (Vitamin B_6)

Pyridoxine has often been referred to as an "anti-stress" vitamin because of its role in hormone biosynthesis, energy production, and neurotransmitter formation. Because of its role in neurotransmitter formation (e.g., GABA, serotonin), pyridoxine helps to regulate mood, sleep, eating habits, and pain.[45-47] A deficiency in pyridoxine may cause insomnia, irritability, and depression. Pyridoxine also plays a vital role in cardiovascular health, and research suggests that pyridoxine may inhibit platelet aggregation, reduce total plasma lipid and cholesterol levels, and enhance HDL cholesterol levels.[48,49] Furthermore, pyridoxine appears to exert an antihypertensive effect through its influence on the sympathetic nervous system, which controls blood pressure.[49] Pyridoxine is water-soluble and has a good safety profile; however, fairly high doses (200 mg/day) taken for an extended period of time may cause neurotoxicity.

Pantothenic Acid (Vitamin B_5)

Pantothenic acid is most widely known for its key role in energy metabolism. In particular, pantothenic acid is converted to coenzyme A—an important catalyst in the breakdown of fats, carbohydrates, and protein for energy. Pantothenic acid also promotes healthy cholesterol levels and supports proper adrenal gland function.[50,51] While overt deficiencies are rare, marginal deficiencies in pantothenic acid may be characterized by fatigue.[52]

TIME-HONORED, HERBAL SUPPORT FOR WOMEN'S HEALTH

The systems of complementary medicine most similar to modern Western medicine are the medical traditions of ancient Greece, Rome, and Europe. Centuries later, these therapeutic systems were combined with the folk traditions of Europeans and Native Americans and utilized by the physicians and midwives who settled in America. During the first 200 years after the settlement of the New World, the principle form of medicine was herb-based. Today, the healing properties of plants are actively researched, and scientists continue to identify principal ingredients with properties corresponding with their documented traditional uses. This is especially true in the area of women's health and menopause.

Black Cohosh

Black cohosh was first introduced to gynecology by Native Americans as early as the 18th century, and continues to be used in the management of peri- and postmenopausal complaints. Popular in Germany, it has been used since the early 1940s and is approved by the Commission E of the German Federal Health Authorities for irregular menstruation, premenstrual discomfort, and menopausal hot flashes.[53-55] Although research has demonstrated the effectiveness of black cohosh in peri- and postmenopausal women, its precise mechanism of action remains inconclusive. Proposed mechanisms include selective estrogen receptor modulator (SERM)-like activity or the ability to selectively modulate LH surges from the pituitary gland.[56,57]

A double-blind, randomized study assessed the effectiveness and safety of black cohosh in 152 peri- and postmenopausal women. Subjects were randomly assigned to receive either 39 mg/day or 127.3 mg/day of black cohosh for a period of 24 weeks. Both treatment groups experienced a significant reduction in menopausal symptoms such as hot flushes, with a responder rate of 70% at 39 mg/day and 72% at 127.3 mg/day. There was no evidence of a systemic estrogenic effect.[58]

In another study, the effects of black cohosh were evaluated in 110 women suffering from menopausal symptoms. Participants received either 40 mg/day of a black cohosh extract or a matched placebo for 2 months. Compared to the placebo, black cohosh was shown to significantly reduce LH levels, with no effect on FSH, suggesting its action was discrete from estrogen receptor regulation. Since elevated LH levels are associated with the occurrence of hot flushes, these findings further support the use of black cohosh in peri- and postmenopausal women.[59] Furthermore, a review of 8 human clinical studies found that black cohosh improved symptoms of menopause comparable to HRT.[60] The application of black cohosh extends beyond its use for the management of menopausal complaints. It has also been used traditionally in women with premenstrual syndrome, functional bleeding irregularities in a broader sense, and other gynecological complaints.[61]

Chasteberry

Chasteberry is an herb native to the Mediterranean region, but now found in subtropical climates around the world. Chasteberry has a rich history of use as a remedy for women, with the first medicinal accounts recorded by Hippocrates in the 4th century B.C. Today, chasteberry is widely used and accepted as a treatment for female complaints such as menopause, PMS, abnormal menstrual rhythm, water retention, and painful breast swelling.

Chasteberry appears to act directly on the pituitary gland to inhibit the secretion of follicle stimulating hormone (FSH) and promote the secretion of luteinizing hormone (LH). This apparent stimulatory effect on LH leads to an increase in progesterone, and may normalize the balance between estrogen and progesterone. Improving the levels of progesterone may be especially useful during pre- and perimenopause when menstrual irregularities are likely to occur. Furthermore, progesterone exerts an antiproliferative protective effect on breast tissue that appears to antagonize the proliferative effects of excess levels of circulating estrogens, which may reduce breast cancer risk.[62] Research suggests that the increased risk for breast cancer occurs in women who produce low levels of progesterone relative to estrogen throughout their reproductive years. Chasteberry may also possess the ability to prolong proges-

terone's positive effects throughout the menopausal transition.

Chasteberry also possesses dopaminergic properties that inhibit the secretion of the hormone prolactin.[63] Relative increases in circulating prolactin have been linked to fibrocystic or painful breasts, water retention, reduced libido, and depression associated with PMS. Treatment with 20 mg of chasteberry extract daily during 3 menstrual cycles has been shown to significantly relieve these symptoms.[64] Elevated levels of prolactin also decrease the life and action of the corpus luteum, and therefore decrease the production of progesterone. Research suggests that chasteberry's progesterogenic effect is, in part, related to its ability to decrease prolactin levels.[65,66]

Ginseng, Licorice, and Holy Basil

Herbal adaptogens—such as ginseng (*Panax ginseng*), licorice (*Glycyrrhiza uralensis*), and holy basil (*Ocimum sanctum*)—can help correct adrenal fatigue and improve the body's adaptogenic response. Similar in benefit, these herbs have all demonstrated normalizing effects on levels of cortisol, a hormone critical in the body's response and resistance to stress.[67-73] Ginseng and licorice have both been shown to inhibit 11β-hydroxysteroid dehydrogenase (11β-HSD), an enzyme responsible for converting cortisol into inactive cortisone, resulting in increased circulating levels of cortisol.[69] Furthermore, the active constituents of licorice, glycyrrhizin and glycyrhetinic acid, are similar in structure to hormones produced by the adrenal cortex, suggesting they possess adrenocorticoid-like activity.[70] Although the mechanism is unknown, holy basil has also been shown to normalize corticosteroid (e.g., cortisol) levels in stress-induced animals.[72,73]

Note: Although ginseng has been historically used as an adaptogen in cancer patients, preliminary in vitro research suggests it may activate estrogen-responsive genes in human breast cancer cells. Women at risk of breast cancer should therefore avoid use.[74]

In light of the recent connection between the possibility of declining adrenal function (adrenopause) and menopausal symptoms, these herbs may provide special benefit, especially as part of a mix of herbs designed to balance female hormones. (For more information about the beneficial effects of adaptogens on the stress response, please refer to the Applied Nutritional Science Report entitled, *Nutritional Management of Stress-Induced Dysfunction* by Richard L. Shames, M.D.)

Dandelion and Stinging Nettle

Stinging nettle (*Urtica dioica*) has been used since ancient times as both a food and medicinal plant for a wide spectrum of ailments. Today it is commonly used as a diuretic, detoxifier, and antihypertensive. Specific to women's health issues, it is also commonly used to relieve premenstrual water retention and provoke menses.[75,76] Some of the traditional medicinal uses of stinging nettle are supported by research on animals.[75-80] In one study, stinging nettle extract was shown to reduce elevated liver enzyme levels, decrease lipid peroxidation, and increase antioxidant activity.[80] Additional research has demonstrated an immediate reduction of arterial blood pressure and heart rate following the perfusion of nettles extract that was accompanied by increases in both diuresis and natriuresis, suggesting an action on both renal function and the cardiovascular system.[76]

Similar to stinging nettle, dandelion (*Taraxacum officinale*) is well known for its use in home recipes and folk medicine remedies primarily for liver and gall bladder dysfunction and water retention. Although research is limited, dandelion has been demonstrated to produce similar effects to nettles in promoting diuresis and antioxidant activity.[81,82] In animal research, dandelion extract was shown to have diuretic activity comparable to that of furosemide.[82] As a rich source of potassium, dandelion is also capable of replacing potassium lost through diuresis. In addition, dandelion extract has demonstrated free radical scavenging activities in vitro.[81] Due to the overlapping effects of dandelion and nettles, these two plants may be more effective when used in combination.[77]

Valerian, Motherwort, and Lemon Balm

Additional herbs to consider are those with mild sedative activity. Women who experience insomnia, tension, or anxiety with menopause may find some relief with herbs such as valerian root (*Valeriana officinalis*), lemon balm (*Melissa oficianalis*), or motherwort (*Leonurus cardiaca*). Traditionally, motherwort was commonly prescribed for women with menstrual disorders to provoke menstruation, and more recently has been employed as a nerve tonic and sedative.[83] Lemon balm is known to increase calmness and is currently used as a sleep aid; it has also been traditionally used to enhance memory.[84-86] Valerian is also well known for its sedative and sleep-promoting properties.[53]

LIFESTYLE CONSIDERATIONS FOR MAINTAINING OPTIMAL HEALTH

Differentiating between those risk factors that are non-modifiable (e.g., heredity, family history) and those that are modifiable (e.g., diet, lifestyle) is an important step in determining the best strategies for relieving hormone-related symptoms and preventing disease. The following lifestyle choices are known to play a significant role in reducing the overall risk to menopausal discomfort and age-related disease.

- Exercise reduces hot flushes, promotes healthy bone density, and improves mood.
- A lowfat diet that is rich in fiber, antioxidants, and omega-3 fatty acids helps to lower the risk to heart disease and cancer.
- Quitting smoking is important for several reasons. Research has shown that women who smoke experience menopause earlier than women who don't. Smoking also increases the risks of heart disease and osteoporosis.
- Excessive caffeine and alcohol consumption have been shown to negatively affect bone health.
- Elevated stress levels are associated with an increased risk of heart disease and a reduced immune response.

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Natural Support for Premenopause and Beyond: A Summary

BY JOSEPH L. MAYO, MD, FACOG

Menopause is a normal transition preceded by hormone changes during the late premenopause and perimenopause years. Late premenopause refers to the period between the ages of 35 to 40, a time when some women begin to experience the first signs of changing hormone levels. However, most women experience the first signs of approaching menopause between the ages of 40 and 51, a period known as perimenopause. The actual onset of menopause, which is characterized by a cease of menstruation for one year, occurs in most women by age 50 to 51, after which women are considered postmenopausal.[1,2]

Over one-third of women in the United States are experiencing or have been through menopause, many of whom have endured symptoms of hormonal changes. The most common symptoms are hot flashes, which are estimated to occur in 6% to 63% of premenopausal women; 28% to 65% of perimenopausal women; and 93% of women in their first two postmenopausal years. The pattern and intensity of symptoms may vary greatly, and many women are also challenged with a barrage of other hormone-related complaints (Table 1).[1,3]

Table 1. Signs and symptoms of the menopause transition.

- Hot flushes/night sweats
- Irregular menstrual bleeding
- Decreased vaginal lubrication
- Painful intercourse
- Depression and mood swings
- Memory loss
- Sleep disturbances
- Cold hands and feet
- Weight gain
- Urinary incontinence
- Loss of libido
- Headaches

TRANSITIONAL HORMONE CHANGES

During the ten to fifteen years before menopause, estrogen and progesterone levels begin fluctuating and can become out of balance with each other. In the last year preceding the onset of menopause, estrogen levels decrease very rapidly. This decline in estrogen, along with other sex hormones, prompts the onset of menopause.[1,4]

Influences on Women's Health

The changes in hormone levels that occur during the menopause transition may cause more than undesirable symptoms; they may also contribute to disease risk and functional disorders. Women who are already at an increased risk because of genetics, illness, or poor dietary and lifestyle choices should be especially concerned.

Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding (DUB) is a functional problem that commonly occurs during perimenopause, with greater that 250% of cases in women over age 40. DUB is characterized by irregular menstrual bleeding that may be more or less frequent, lighter or heavier, shorter or longer in duration, or spotting between menstrual cycles. It is important for women with irregular menstrual bleeding to have a thorough medical assessment. Other types of irregular menstrual bleeding may be associated with a serious medical condition.[8,9,10]

Osteoporosis and Heart Disease

Heart disease and osteoporosis are very prevalent in postmenopausal women. Both of these diseases are strongly linked to the decline in hormone levels associated with menopause. Unhealthy dietary and lifestyle factors such as inadequate calcium and vitamin D intake, lack of exercise, excessive alcohol and caffeine consumption, and smoking also increase disease risk.

NUTRITIONAL SUPPORT FOR WOMEN'S HEALTH

Nutritional support for women from premenopause and beyond should include natural ways to support hormone balance, as well as ways to help reduce the risk of osteoporosis and cardiovascular disease.

Soy Isoflavones

Soy isoflavones are plant compounds that have weak estrogenic action in the body. According to research, they appear to protect against menopausal symptoms, as well as osteoporosis and cardiovascular disease. For those patients who may be allergic to soy, isoflavones are also found in the herbs red clover and kudzu root.[25-30]

Calcium

It is well known that adequate calcium intake helps to prevent the excessive bone loss that is associated with osteoporosis. In addition to calcium, vitamin D and minerals such as magnesium and boron are recognized as important nutrients in maintaining bone strength throughout the menopausal years.[34-37]

Vitamins C and E

Vitamins C and E are important antioxidants that support cardiovascular health and immune function. Some women may need higher levels of these vitamins due to lifestyle factors or certain health issues.[38-41]

HERBAL SUPPORT FOR THE MENOPAUSE TRANSITION

The systems of complementary medicine are well documented, with the use of herbs in medical practice dating back centuries. Today, the healing properties of herbs are actively researched, and scientists continue to validate their historical uses.

Black Cohosh

Black cohosh is a time-honored herb that was first introduced to gynecology as early as the 18th century. Modern research supports its use in the management of peri- and postmenopausal complaints. Popular in Germany, it has also been approved by German health authorities to be used for irregular menstruation, premenstrual discomfort, and menopausal hot flashes.[53-61]

Chasteberry

Chasteberry has a long history of use as a women's remedy, with the first medicinal accounts recorded by Hippocrates in the 4th century B.C. Today, chasteberry is widely used and accepted as a treatment for female complaints such as menopause, PMS, abnormal menstrual rhythm, water retention, and painful breast swelling.[63-66]

Dandelion and Stinging Nettle

Stinging nettle has been used since ancient times as both a food and medicinal plant for a wide spectrum of ailments, including premenstrual water retention and for provoking menses.[75-82] Similar to stinging nettle, dandelion (*Taraxacum officinale*) has a long history of use as a natural diuretic. Due to the overlapping effects, these two plants may be more effective when used in combination.[77]

Valerian, Motherwort, and Lemon Balm

Additional herbs to consider are those with mild sedative activity. Women who experience insomnia, tension, or anxiety with menopause may find some relief with herbs such as valerian root, lemon balm, or motherwort.[53,83-86]