

MENOPAUSE

I. Physiology of Menopause

- Menopause refers to the cessation of menstruation due to the depletion of ovarian follicles. Prior to actual ovarian failure, there is a decline in ovulatory function with fewer follicles present. Thus, there is a decline in ovarian estrogen and inhibin production. With falls in ovarian hormones, there is less negative feedback on the pituitary and hypothalamus, and there is a detectable rise in follicle stimulating hormone and luteinizing hormone. A serum follicle-stimulating hormone (FSH) level is the most sensitive test to confirm menopause.
- The physiologic period of waning ovarian function is called the climacteric. It generally lasts for several years before atresia of all estrogen-producing follicles has occurred.
- In the United States, menopause is said to occur normally between ages 45 and 55, with the median age being 51. Menopause prior to age 40 is termed premature menopause; after age 55 it is termed late menopause. The onset of menopause is genetically related. It is not related to age at menarche, number of pregnancies, age of last pregnancy, oral contraceptive use, or use of infertility medications. Menopause may occur earlier in women who have a history of tobacco use.

II. Changes Associated with Estrogen Decline

- Numerous physical and psychological symptoms have been attributed to the decline and discontinuance of ovarian function in midlife. These symptoms include vasomotor symptoms, genital atrophy, osteoporosis, menopausal skin changes, cardiovascular disease, psychiatric disorders, and changes in sexual satisfaction.

A. Vasomotor Symptoms

- Vasomotor symptoms, or hot flashes, are the most common perimenopausal symptoms that compel women to seek medical attention. Seventy-five percent of women experience hot flashes. The average duration of these symptoms is two to three years.
- These symptoms, which include sudden increases in central skin temperature as well as perspiration, are apparently due to deregulation of the temperature-regulating center in the hypothalamus. Both peripheral vasodilatation and perspiration occur. The flush, which generally lasts from a few minutes to 20 minutes, typically is preceded by a premonition - a flash. It is apparently related to decreases in estrogen and inhibin levels, not to absence of estrogen.
- About one-third of women with vasomotor symptoms find these symptoms severe enough to require medical assistance. Hot flashes may begin before menopause, but generally are more severe after cessation of menses.

- Exogenous estrogen therapy, progestogen therapy, and, to a lesser extent, vasodilator therapy have been shown to decrease the incidence of vasomotor symptoms. Flushes may not respond optimally to estrogen replacement therapy for up to one month.

B. Genital Atrophy

- Genital atrophic changes associated with hypoestrogenism are a significant problem for many women. Clinically, the atrophic vagina has a pale appearance and loses its elasticity. The epithelium is thin and friable, and with the lack of colonization by acidophilic bacteria, it no longer produces glycogen.
- The symptoms related to genital atrophy include vaginal and vulvar itching and burning, dyspareunia, vaginal bleeding, dysuria, urinary frequency, and urinary urgency.
- The most effective therapy for atrophic vaginitis or urethritis is estrogen, which increases the local blood supply and in part reverses these changes.

C. Osteoporosis

- Osteoporosis, defined as a reduction of bone mass per unit volume, significantly affects more than one-third of older women.
- Bone strength or bone mineral content is a function of numerous factors that, when deficient, may predispose one to develop osteoporosis. Osteoporosis is rare in African-American women, and it is more common in thin Caucasian or Asian women.
- Osteoporosis may be somewhat less common in women who have maintained healthy lifestyles. Smoking, excessive alcohol use, sedentary lifestyle, and steroid use appear to be contributing factors in women who develop osteoporosis.
- There is well-documented accelerated bone calcium loss beginning prior to the time of ovarian failure. The calcium loss is primarily from the trabecular (spongy) bone of the vertebral bodies, long bone shafts and heads, and the pelvis. Abundant evidence indicates that exogenous estrogen therapy reduces the risk of postmenopausal osteoporosis and fractures.
- Serial bone densitometry studies show a halt in bone density loss in estrogen-treated patients but not in untreated controls.

D. Menopausal Skin Changes

- The skin changes associated with aging include increased fragility and wrinkling, as well as some changes in sensation. These changes may increase around the time of menopause. A decline in skin collagen content paralleling the decline in bone density in postmenopausal women has been illustrated with a loss of up to 3 percent per year. Estrogen therapy slows the loss of collagen.

E. Cardiovascular Disease

- In the United States, heart disease - specifically coronary artery disease (CAD) - is the leading cause of death for postmenopausal women. Numerous epidemiologic studies indicate that hormone replacement, particularly estrogen replacement, after ovarian failure substantially reduces the incidence of coronary artery disease.
- Ovarian failure may also be an important determining factor in coronary artery disease in women. The incidence of the disease in women prior to menopause is much lower than that in men of the same age.
- More remains to be learned about hormone replacement therapy and heart disease. Currently, several randomized clinical trials are under way with CAD as the end point. These studies will ultimately quantify the benefit of estrogen replacement therapy with far more certainty than present case-controlled and cohort studies.

F. Psychological Disorders

- A number of symptoms (anxiety, depression, irritability, fatigue, insomnia, emotional lability, and changes in libido) may occur around the time of menopause. The etiology of these symptoms is incompletely understood and appears to be multifactorial.
- Estrogen decline may indirectly cause or worsen these symptoms by increasing the risk of developing a sleep disturbance and adversely affecting overall feelings of well-being. The use of HRT in menopausal patients has been demonstrated to help improve symptoms such as nervousness, depression, anxiety, and insomnia. In addition, progestin therapy may increase depressive symptoms.
- As longevity of women increases, so does the prevalence of senile dementia. It is estimated that up to 50 percent of women 85 years or older may suffer from Alzheimer's disease.
- Overall, patients with mild to moderate dementia have demonstrated improvement of memory, orientation to place and time, and mental calculations. Estrogen replacement therapy has also been demonstrated to reduce the number of women who develop Alzheimer's disease.

III. Symptoms Not Directly Related to Estrogen Depletion

A. Androgens and Menopause

- Recently, much has been presented in the lay press concerning the use of androgens, such as dehydroepiandrosterone (DHEA), as an energy boost and sexual aid. As a brief review, androgens are produced by both the ovary and the adrenal gland.

- Circulating levels of both decline 50 percent between the third and fifth decade of life. DHEAS levels decline with age.
- The addition of androgens to estrogen replacement therapy may possibly aid in the treatment of menopausal women's psychological symptoms (i.e., anxiety and depression), and may help prevent bone reabsorption as compared to estrogen alone.

B. Libido

- When a woman complains of decreased libido, more than androgen levels need to be considered.

C. Hormone Replacement Therapy

- There are essentially five indications for the use of HRT: treatment of vasomotor symptoms; treatment of atrophic vaginitis; reduction of cardiovascular disease; prevention of osteoporosis; and management of menopausal-related psychosomatic complaints.
- Because women live much longer today and spend at least one-third of their lives after menopause, estrogen deficiency and its treatment have become much more significant issues than they were in the early 1900s.
- "Glandular therapy" can be traced back to ancient Egyptian times, the first real attempts to treat symptoms of ovarian failure with "ovarian secretions" did not occur until 1885. It was in the 1920s and 1930s that estrogens in the urine of pregnant mares were discovered to be active when given to humans, and that estrogens could be produced synthetically in forms that could be absorbed and remain active when given orally.

D. Benefits

- It is now clear that estrogen given to postmenopausal females in doses that produce serum levels of active estrogens biologically equivalent to the lowest levels seen in women of reproductive age will effectively treat vasomotor symptoms and genital atrophy, will prevent up to one-half of cases of osteoporosis, and will possibly decrease mortality from coronary artery disease by 40 to 50 percent.

E. Endometrial Effects - Rationale for Progestin Therapy

- Numerous epidemiologic studies have shown an increase in adenocarcinoma of the endometrium with use of exogenous estrogens without progestin after menopause.
- Experimental evidence indicates that administration of estrogen without progesterone to postmenopausal women, even in low doses, will produce early forms of hyperplasia in 20 to 35 percent within a year's time.

- Exogenous progestins prevent hyperplasia in postmenopausal women receiving estrogens. In addition, administration of progestins decreases the incidence of endometrial cancer.

F. Other Cancer Risks

- Cancer of the breast is the most frequent cancer in women, and the second leading cause of cancer death. The median age at which breast cancer develops is 69, but 80 percent of women are affected after the age of 40. There is an abundance of indirect evidence that estrogen and/or progesterone have roles in breast cancer etiology.
- The FDA Advisory committee has agreed that long-term use of estrogen is associated with a modest increase in breast cancer risk of a magnitude of 1.3 to 1.5; however the risk may be significantly lower if lower doses of estrogen are used consistently. In addition, the risk may increase further when women already at high risk for breast cancer take exogenous estrogen.

G. Benign Breast Problems

- Fibrocystic breast changes respond variably to menopausal hormone replacement. As with other hormone-related effects, breast symptoms usually are dose-related, and mastalgia frequently worsens during the estrogen/progestin days of cyclic therapy.

H. Other Effects (Coagulation, Hypertension, Vascular Disease, and Gallbladder Disease)

- By directly or indirectly stimulating liver enzymes, estrogen may increase the production of serum globulins, including angiotensinogen, sex hormone binding globulin, and others. It favorably affects fat and cholesterol metabolism in the liver, tilting the balance toward increases in high-density lipoprotein cholesterol and triglycerides, and decreases in total cholesterol and low-density lipoprotein cholesterol.
- Estrogen also increases the cholesterol content of bile, and may increase the incidence of cholesterol-containing gallstones in some individuals.

I. Estrogens

- The most commonly used oral estrogen preparation is conjugated equine estrogens (Premarin). Tablet strengths are 0.3, 0.625, 0.9, 1.25, and 2.5 mg.
- Unopposed estrogen therapy appears to be the optimal regimen for patients who have undergone hysterectomy; but for women with a uterus, a progestin is important to reduce the risk of endometrial hyperplasia and cancer.
- The estradiol and estrone levels produced by most of these regimens, as well as by equivalent doses of other oral medications, either are lower than or biologically equivalent to blood levels seen in reproductive-aged women.

- Administration of estrogen every day with no days off may produce less withdrawal bleeding and may possibly have a more beneficial effect on the bone and heart.
- The disadvantages of cyclic therapy include both bleeding and the progestin-related side effects of bloating, GI disturbances, and premenstrual symptoms.
- Continuous combined regimens utilize the same estrogen doses. The advantage of these regimens include absence or very low incidence of progestin related side effects and the potential for amenorrhea due to the progestogen's ability to inhibit endometrial proliferation.