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Current Approach to Menopause

Menopoza Güncel Yaklaşım

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ABSTRACT

With the increase in the life span, the period of physiological menopause also extends. Many health problems, especially vasomotor symptoms, will develop in the period of menopause. Therefore, the medical and paramedical methods developed are frequently updated. While not being prescribed as often as in previous years, hormone replacement therapy is currently the most important method for relieving these symptoms.

Key Words: Menopause, hormone replacement therapy, vasomotor symptoms

ÖZET

Yaşam süresinin artması ile fizyolojik menopoz dönemi de uzamıştır. Vazomotor semptomlar başta olmak üzere bir çok sağlık sorunu gelişecektir. Tüm bunlara karşın geliştirilen medikal ve paramedikal yöntemler sık olarak güncellenmektedir. Önceki yıllarda olduğu gibi sık reçete edilmemekle beraber hormon replasman tedavisi halen bu semptomların giderilmesinde en önemli yöntemdir.

Anahtar Kelimeler: Menopoz, vazomotor semptomlar, hormon replasman tedavisi

Introduction

Menopause, diagnosed by the absence of bleeding for at least one year after the last menstrual bleeding, negatively affects the quality of life of women. With the prolongation of the average life span, especially in the developed countries, increasing demand for quality living of the elderly population came to the forefront. However, the increase in life span did not change the mean age of menopause (1). The average age of menopause is 51. Physiologic menopause occurs as a result of atresia of a large part of the oocytes. Artifical menopause caused by surgical removal of ovaries or over dysfunction after radiotherapy and chemotherapy. Menstrual irregularity is prevalent in the perimenopausal period, which lasts about 2-8 years. Menstrual bleeding followed by a pattern of gradual decrease in the amount and duration of the bleeding and then a cut, and sudden interruption is uncommon (1,2). As age progresses, cycle lengths become shorter. At the beginning of the perimenopausal period, the follicular phase is short and the polymorphism is dominant and the luteal phase defect results in oligomenorrhea (3). There is a stabilizing increase in FSH due to reduced ovarian reserve and reduced inhibin levels in premenopausal women. Thus, estrogen levels are increased by folliculogenesis of the yet not depleted follicles, but LH and progesterone levels do not change. In this period, contraception should not be neglected (4).

In the postmenopausal period following 12 months of last menstrual period, follicles that are almost completely exhausted do not respond to increased FSH and the amount of ovarian steroid decreases and the amount of estrogen decreases to 10-20 pg / ml. In contrast, gonadotropins rise and FSH levels peak after 1-3 years from menopause (4). The estrogen (E1), which is synthesized by the peripheral aromatization of androstenedione in the basic estrogen peripheral tissues in the postmenopausal woman while the basic estrogen in the circulation in the premenopausal period is estradiol (E2). E1/E2 ratio increases in postmenopausal women. Estrogen levels become directly proportional to the amount of fat tissue after functional overexpression of the ovaries after menopause (3,4).

In the premenopausal phase, 45% of the circulating androstenedione and 25% of the testosterone are expressed from overs, whereas in the postmenopausal phase, 80% of the circulating androstenedione is adrenal, 20% over. In the postmenopausal period, ovaries secrete androgen mainly. Postmenopausal testosterone synthesis

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from overs continues to decrease slightly as a result of the stimulating effect of the increased gonadotropins on the stromal cells. While this reduction is minimal in spontaneous menopause, in surgical menopause it is massive. The level of androstenedion is the same during the first few years after the change then it is reduced by %50 following years. Another source of androgens in postmenopausal women is the adrenal gland. In later ages, DHEA 60% and DHEA-S 80% decrease, which is called adrenopause. Since ovulation does not occur in postmenopausal period, progesterone levels are low while estrogen is at a certain level. Therefore, there is a risk of endometrium and breast cancer in the postmenopausal period (5,6). Vasomotor symptoms develop faster and louder in artificial menopause than physiological menopause. Osteoporosis and cardiovascular disease risk are higher in patients who went to oophorectomy. The loss of ovarian function and reduced estrogen levels cause many symptoms that negatively affect quality of life, such as hot flushes in women, night sweats, mood swings and sleep disorders. Long-term estrogen deficiency may also lead to life-threatening conditions like cardiovascular disease and osteoporosis. The incidence of severe vasomotor symptom inconvenience in postmenopausal women is 60-80%, which often affects women's quality of life (7). Moderate and severe vasomotor symptoms usually start with menopause and last an average of 10 years. Vasomotor symptoms affect 75% of perimenopausal women. Moderate and severe symptoms are most commonly seen in ages 45-49. The most common symptom among vasomotor symptoms is the hot flush symptom, which can be explained by thermoregulatory events, which are caused by menopausal changes, including estrogen deficiency or estrogen surge (8). This leads to peripheral vasodilatation and sweating. This is not the case when LH is elevated during hot flush because vasomotor symptoms also occur in patients with pituitary gland removed. Vasomotor symptoms are due to estrogen depletion. Symptoms of hot flushes in primary estrogen deficiencies are not seen (4). Previous studies have shown that obesity may be a protective effect against vasomotor symptoms because testosterone is aromatized with estrogens in the adipose tissue (9). However, recent studies have shown that obese women report more vasomotor symptoms than thinner women. Increased body fat rate may cause these symptoms by increasing body temperature (10, 11). There was also a relationship between vasomotor symptoms and high BMI and waist circumference. Thus, obesity can be considered as a common factor for metabolic syndrome and vasomotor symptoms. Postmenopausal women with vasomotor symptoms generally have a worse lipid profile than women without symptoms (10,12,13).

Menopause, the end of fertility, is experienced by each individual with different characteristics. The hot flush the most common symptom, was seen in 60% of women aged 50-54 who participated in the WHI study (Women's Health Initiative). This prevalence decreases with age. It found this prevalence is 15% between the ages of 55-59, 6% between the ages of 60-69 and 3% over the age of 70 (14). Culture and diet can affect the severity of symptoms. Japanese women who have traditionally been fed a low-fat diet and whose vasomotor symptoms are less frequent, have found 10 times more phytoestrogen concentrations in urine than female American and Finnish women (15). The low prevalence of hot flushes in Japanese women may be related to excessive intake of phytoestrogens and less meat consumption; but some SWAN (Study of Women's Health Across the Nation) data suggest that ethnic changes may be explained by gene polymorphism (16). In menopausal women, there are significant changes in blood lipid levels. Compared with premenopausal women, total cholesterol, LDL and triglyceride levels have been shown to increase in postmenopausal women, while HDL levels have been shown to decrease which is associated with increased risk of cardiovascular disease (17). The prevalence of metabolic syndrome increases with menopause. The increased risk of cardiovascular disease with menopause is further increased by the metabolic syndrome (18). Many treatment methods have been developed to relieve complaints of vasomotor symptoms. Hormone replacement therapy (HRT) is often the most effective treatment for reducing symptoms like hot flushes, night sweats and insomnia, sexual desire. Sleep disorders associated with menopause become worse with night sweats (7). Vaginal dryness, pruritus and dysparonia are frequently seen in postmenopausal women and are associated with decreased estrogen levels. Vaginal atrophy may also develop. It occurs in 10-50% of menopausal women. Dryness, paleness, and reduced vaginal mucosa ruges are physiological changes that can be seen in postmenopausal women. However, these can lead to pruritis, dyspareunia and urinary system infections. (19).

Treatment options for vasomotor symptoms (4);

- Hormone therapy (estrogen, combined estrogen / progesterone, progesterone)
- Prescription nonhormonal drugs (clonidine, gabapentin, selective serotonin and norepinephrine reuptake inhibitors)
- Non-Prescriptive drugs (isoflavone, soy products, blackcohosh, vitamin E)
- Lifestyle changes (reducing body temperature, maintaining healthy weight, smoking cessation, regular breathing)

In the WHI study, invasive breast cancer, the risk of coronary heart disease, cerebrovascular accident, pulmonary embolism, dementia increased while the risk of hip fracture and colorectal cancer decreased in the group receiving estrogen and progesterone. WHI and HERS (The Heart and Estrogen / Progestin Replacement Study) studies have not shown that combined HRT reduces cardiovascular disease risk (20). The WHI study did not find an increased risk of coronary heart disease in women who received HRT within the first 10 years of menopause or between the ages of 50-59 (21). In the group receiving only estrogen, the risk of deep vein thrombosis and cerebrovascular accident are increased. The risk of hip fracture is reduced. The risk of coronary heart disease, invasive breast cancer, and colorectal cancer has not changed (20).

Perimenopausal women benefit from oral contraceptives in vasomotor symptom treatment. High doses of estrogen and progesterone in oral contraceptives both alleviate vasomotor symptoms and control for cyclic menstrual bleeding. Low dose oral esterified and conjugated estrogens (0.3 mg / day) or transdermal estradiol (0.025 mg / week) are often effective. Progesterone therapy should also be added to women who have not undergone hysterectomy (23, 24). Because vasomotor symptoms are caused by estrogen discontinuation rather than estrogen deficiency, when the HRT is initiated, the dose should be taper off while it is stopped. If the patient refuses to take estrogen or if there is a contraindication, only progesterone therapy is a choice. Medroxyprogesterone acetate (MPA 20mg / day) and Megesterol acetate (megace 2x20mg / day) may be given (25).

HRT indications are vasomotor symptoms, urinary system atrophy, genital system atrophy, osteoporosis prophylaxis and treatment. Known contraindications to HRT are known or suspected breast cancers or endometrium cancers, unrecognized uterine bleeding, acute thromboembolic diseases, liver dysfunctions, acute biliary cirrhosis, and hypertriglyceridemia above 500 mg / dL. Drugs that reduce central neuro-pathologic tonus such as clonidine may be beneficial in hot flushes.

Clonidine has been shown to significantly reduce vasomotor symptoms at randomized placebo-controlled trials. It can be used either orally (0.1-0.2 mg / day) or weekly transdermal patches (0.1 mg / day) (26). Selective serotonin reuptake inhibitors (SSRIs) are also effective in relieving symptoms of hot flashes, but studies have shown different results with different drugs and that all SSRIs are not effective in eliminating vasomotor symptoms. In a double-blind, placebo-controlled study, paroxetine (12.5 and 25 mg / day) reduced both the frequency and severity of vasomotor symptoms in women with menopause (27). Venlafaxine (75 mg / day) also significantly reduced the symptoms of hot flushes compared with placebo (28). On the other hand, a double-blind study with fluoxetine and citalopram (10-30 mg / day) did not show a different improvement from placebo in vasomotor symptoms (29). Gabapentin has been shown to reduce vasomotor symptoms compared with placebo in a randomized controlled trial (30). Bellergal, which includes ergotamine, phenobarbital and belladonna alkaloids used in the treatment of migraine, has also been shown to reduce vasomotor symptoms (31). Vitamin E (800IU / day) was found to be minimally effective in hot flush complaints in a placebo-controlled study (32).

Cardiovascular disease is the most important cause of death in women and accounts for about 45% of mortalities in women (33). In the WHI study, combined HRT has been shown to increase the risk of cardiovascular events in healthy women, as it does not reduce cardiovascular risk in women with cardiac disease (34).

Estrogen is still the most effective and expressive treatment for vasomotor symptoms and reduces hot flushes by 80-90% (4). However, stroke, thromboembolic event, biliary tract diseases and urinary incontinence are associated with increased risk (35).

Hormone therapy in women with uterus should include progestin as well as estrogen to protect against endometrial hyperplasia and cancer. Treatment regimen could be continuous daily estrogen and progestin or cyclic regimen. In the cyclic regime; Estrogen and progestin are used for

25 days and 5 days are discontinued, or progestin is added for 1-21 days on estrogen 7-21 days and discontinued for 7 days (36).

Transdermal and topical gel oestrogens recommended for women who have high thrombotic risk, who use other medications, have triglyceride levels at their limit, gallstones, or do not use daily pills are less likely to have first-pass effect and therefore carry less thromboembolic risk than oral estrogens (37).

They compared bone mineral density between women with and without vasomotor symptoms in postmenopausal women. In patients with vasomotor symptoms, bone mineral density was found to be significantly lower for the vertebra and femur neck when compared to groups without vasomotor symptoms (38,39).

Endometrial biopsy should be performed in the postmenopausal period if there is an uterine bleeding whether HRT is taken or not. Endometrial biopsy should be performed if the endometrial thickness of the double wall is 5 mm or more, or if the endometrial irregularity is present in the follow-up ultrasound imaging in the absence of hemorrhage (40, 41).

Significant complications of HRT; endometrium cancer, breast cancer (longer than 5 years, especially in combined HRT), myocardial infarction (in combined HRT), stroke, venous thromboembolism (no increased risk for transdermal preparations), cholelithiasis, alzhemier, dementia and adverse effects on cognitive functions (35).

Although HRT is not an easy choice, there is currently no effective treatment for vasomotor symptoms. Especially women in the first decade after menopause and women younger than 60 years should be preferred with the lowest effective dose and the shortest course of treatment.

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