



Review Article

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Menopausal Hormone Replacement Therapy



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Abstract

Estrogens and Progesterones in various forms and modalities either alone or in combination have been used to treat menopausal symptoms including postmenopausal osteoporosis and osteopenia. However, recent evidence suggests that they should be used judiciously and in an individualized manner to optimize benefits and reduce risks to our patients.

Keywords: MHT; Menopause; Hormone therapy; Estrogens; Progesterones

Abbreviations: MHT: Menopausal Hormone Therapy; EPT: Estrogen Progesterone Therapy; FSH: Follicle Stimulating Hormone; LH: Luteinizing Hormone; MPA: Medroxy Progesterone Acetate; NE: Norethindrone

Review

Menopause is defined as a normal change in a woman's life when her periods stop for 12 months in a row. This usually happens when they reach the age of 45-55. This state of menopause is due to severe reduction of follicular activity within the ovaries and is associated with reduced production and secretion of estrogen and progesterone. This will trigger a negative feedback increase in hypothalamic secretion of FSH and LH resulting in elevated serum level of these two hormones.

The episodic increased release of these hypothalamic hormones and the decreased levels of estrogens are associated with several menopausal symptoms with variable degrees. Estrogens are believed to play a role in body's thermoregulation by modulating the neurotransmitters in the brain. Symptoms of decreased estrogens in the post menopausal state may present as hot flashes, night sweats, vaginal dryness and pain during intercourse, urinary changes such as frequency and urgency, and osteopenia or osteoporosis.

Naturally, estrogen replacement has been used to treat these symptoms. Estrogens can be prescribed as oral, cream, dermal patch, gel or implant. The estrogens may be conjugated equine estrogens, or synthetic micronized 17 beta estradiol, or ethinyl estradiol.

The use of progesterone along with estrogens was popularized in mid 1975 to prevent the risk of developing endometrial carcinoma while on unopposed estrogen therapy

[1]. The progesterones used are medroxyprogesterone acetate (MPA) and norethindrone (NE).

Subsequently, various MHT regimens have been tried and include: Daily estrogen, cyclic or sequential when progesterone is added for 10-14 days every 4 weeks, and continuous combined estrogen and progesterone combinations.

While MPA is endometrial protective, it was associated with an excess risk of CHD and breast cancer when administered with conjugated estrogen in the WHI [2]. In addition, regimens using continuous versus cyclic MPA may be associated with a higher risk of breast cancer [3]. These findings are also further corroborated by the recent NICE study on combined MHT in menopause [4]. Obviously in women with hysterectomy there was no need for further treatment with progesterone [5,6].

In regards with cardiovascular protective effect although the risk profile appears to be more favorable in young women taking unopposed estrogen, use for prevention is still not warranted [7]. The hormone regimen studied in the WHI was conjugated estrogens and MPA. While it is possible that other estrogen or progestin formulations or doses might not have the same negative cardiovascular effects as conjugated estrogen and MPA, data to support their use for prevention are not available. A most recent review using Cochrane database for the role of MHT and prevention of cardiovascular disease [8] also does not support use of estrogens nor progesterone for this purpose.

Although MHT had been recommended for prevention and treatment of Osteoporosis [2,9,10], estrogen and/or progesterone is no longer recommended for the treatment or prevention of osteoporosis in postmenopausal women because of the increased risk of breast cancer stroke, and blood clots [2].

For women who choose estrogen or combined MHT, short-term use is suggested (generally not more than five years or not beyond age 60 years [11]. However, hot flashes persist for an average of 7.4 years, and many women continue to have symptoms for more than 10 years. Some women with persistent symptoms choose longer-term therapy. For women who experience recurrent, bothersome hot flashes after stopping estrogen, non-hormonal options are recommended before resuming estrogen. For those who do not get adequate relief with non-hormonal therapies, extended use of hormone therapy may be considered.

Discussion

Estrogen should be administered continuously as opposed to the past regimens where estrogen was administered days 1 to 25 of the calendar month. Women will often get hot flashes during the days off, and there is no known advantage to stopping for several days each month.

Since all types and routes of estrogen are equally effective for hot flashes, oral estrogen in the form of conjugated equine estrogens starting at 0.3mg/d is recommended route of treatment because of low cost and ease of use [12]. It can be increased incrementally at 0.15mg/d to adjust for relief of hot flashes although this dosage may also be enough for relief of vaginal and genitourinary symptoms. Vaginal route of administration in the form of vaginal cream may be more effective for relief of vaginal and genitourinary symptoms. Transdermal 17-beta estradiol patch is particularly important in women with hypertriglyceridemia or risk factors for thromboembolism. However, the baseline risk of both venous thromboembolism (VTE) and stroke is very low in otherwise healthy, young postmenopausal women.

All women with an intact uterus need a progestin in addition to estrogen to prevent endometrial hyperplasia, which can occur after as little as six months of unopposed ET. Women who have undergone hysterectomy should not receive a progestin, as there are no other health benefits other than prevention of endometrial hyperplasia and carcinoma. The most extensively-studied formulation for endometrial protection is the synthetic progestin used in the WHI, MPA (2.5 mg daily). Lower dose preparations that contain 1.5mg/d with either 0.3 or 0.45 mg/d of CEE are becoming increasingly popular.

MHT is not recommended for the prevention of CHD, even in young postmenopausal women. Although the risk profile appears to be more favorable in young women taking unopposed estrogen, use for prevention is still not warranted.

Likewise, MHT is no longer recommended for prevention nor treatment of osteoporosis. However, estrogen may be an

appropriate treatment for prevention of osteoporosis in young women whose ovaries do not make estrogen. This treatment may be given as a skin patch or orally, such as a birth control pill.

Furthermore, currently MHT is not recommended for preventive treatment for cognitive function and dementia.

Common side effects of estrogen include breast soreness, which can often be minimized by using lower doses. As noted above, some women experience mood symptoms and bloating with progestin therapy. Vaginal bleeding occurs in almost all women receiving cyclic estrogen-progestin regimens and is common in the early months of a continuous estrogen-progestin regimen. Other side effects include headaches, mood changes, and nausea. If these symptoms cannot be treated with lower doses of MHT or become intolerable, then they should be discontinued.

In addition, MHT's are contraindicated in patients who may be pregnant, have problems with vaginal bleeding, have had breast or uterine cancer, history of stroke, heart attack or thrombophilias, liver disease, or heart disease.

The US Food and Drug Administration (FDA) now requires the adding of labels to all estrogen and estrogen-progestin products warning of the possible risk of heart disease, stroke, and cancer [13].

Both the North American Menopause Society [13] and the American College of Obstetrics and Gynecology agree that use of MHT should be individualized and not discontinued solely based upon patient age. Over 40 percent of women ages 60 to 65 years have persistent hot flashes that can impair sleep and quality of life. They suggest that extended use of MHT (beyond age 60 or even 65 years) may be reasonable when the clinician and patient agree that the benefits of symptom relief outweigh the risks.

The only exception to the above recommendations is the use of vaginal estrogen or other nonestrogen therapies at any age for prevention or treatment of the genitourinary syndrome or menopause [14].

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