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POSTMENOPAUSAL HORMONE REPLACEMENT THERAPY – A REVIEW

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ABSTRACT - Postmenopausal Hormonal Replacement Therapy (HRT) can improve the symptoms like hot flushes,night sweats,insomnia and vaginal dryness, if given for short term. Long team disabilities of osteoporosis can be prevented by giving HRT for long duration. But long term usage of HRT is associated with risks like endometrial cancer and breast cancer .Venous thromboembolism and cardiovascular risks are also found to be increased with its use. So ,to use or not to use HRT is one of the most complex and difficult healthcare decisions and should be made ,weighing all the benefits and risks, that too on a short time basis. Life style changes, such as increasing physical activity, smoking cessation and maintaining a healthy diet and emotional support of family may be helpful in controlling symptoms and preventing chronic disease. These days use of alternative therapies like SERMs and STEARs is upcoming which may substitute HRT in some patients.

KEY WORDS
Postmenopausal HRT , CVS risk, endometrial cancer, tibolone

INTRODUCTION

Menopause is that period of life when permanent cessation of menstruation occurs following the loss of ovarian activity. Median age of menopause has been estimated to be between 50 and 52. As there is an increase in life expectancy, the females are now spending one third of their lives in postmenopausal phase. During this period, there is a decline in the estrogen levels produced by ovaries which can lead to multiple symptoms including vasomotor symptoms like hot flushes , night sweats, parenthesis, atrophic changes in vagina , sexual dysfunction, sleep problems, osteoporosis , cardiovascular disease and psychophysiologic effects like fatigue, insomnia, depression and headaches[1].

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The symptoms like hot flushes, night sweats, insomnia and vaginal dryness can be decreased by use of estrogens and long term disabilities of osteoporosis can be prevented by therapy with estrogen and progestin. In 1960 and 70s , estrogen alone was used in postmenopausal women. In 1980s it was found to increase the incidence of endometrial carcinoma due to continuous stimulation of endometrial hyperplasia by unopposed estrogens. It led to the use of hormone replacement therapy (HRT) i.e. an estrogen and a progestin. Estrogen is used for its beneficial effects in postmenopausal problems and progestin to limit the endometrial hyperplasia by decreasing the estrogen receptor content, by increasing the local conversion of estradiol to estrone by progestin (estrone is less potent) and by the conversion of endometrium from proliferative to a secretory state[1].

HRT Regimens-

HRT is given in the following manner-

Postmenopausal (PMN) women with a uterus- Both estrogen and progestin are given.

PMN women who have undergone a hysterectomy and endomentrial carcinoma not a concern - estrogen alone is given.

In the cyclic regimen, estrogen is given for 25 days and then medroxyprogesterone acetate (MPA) is added for the last 10-13 day of estrogen treatment . 5-6 days are without any hormone treatment, during which withdrawal bleeding occurs due to breakdown and shedding of endometrium. [2,3]

The route of administration of the therapy could be oral, transdermal, subcutaneous implants or as a percutaneous patch or gel. It can also be delivered as vaginal cream, pessary or ring. The problems associated with the sequential regimen are side effects related to the doses of progestin such as breast tenderness, fluid retention, bloating and depression . A lower dose of MPA can resolve these symptoms.[2,3] A vaginal ring delivering estradiol and progestin that lasts 4 to 6 months may help in avoiding these problems. Vaginally delivered progestin is distributed preferentially to the endometrium and might control proliferation at dose levels having little systemic effects[4].

A continuous or combined method of treatment improves patient compliance. Continuous presence of progestin allows the use of lower doses. This approach involves the continuous daily dose of progestin (2.5mg) with estrogen (0.625mg conjugated estrogen) calcium supplementation (250 mg bid with meals) and vit D (400 IU) [2,3]. A placebo controlled double blind randomised trial (WISDOM STUDY) concluded that combined hormone treatment even when initiated many years after the menopause, can improve health-related quality of life[5].

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Long term impacts of menopause and present status of HRT

Osteoporosis

After age of 40 , bone resorption begins to exceed formation by about 0.5% per year. This adverse relationship increases after menopause and upto 5% of trabecular bone and 1-1.5% of total bone mass loss occurs per year after menopause , which increases the risk of fracture .Incidence of vertebral fractures is almost 50% of all fractures .

Estrogen therapy stabilizes the process of osteoporosis or prevents it from occurring but long term estrogen use is necessary to reduce the risk of fracture after age 75 [1] .

The protective effect was observed in women who used HRT for 20 months or more . In order to achieve the most effective protection against fracture , HRT should be continued for long periods . The fracture reducing potential of HRT seems to disappear after few months without treatment and is more effective in women who begin therapy at an older age[6].

Studies have demonstrated that a dose of 0.625 mg of conjugated estrogens is necessary to preserve bone density. Risk of vertebral fracture is decreased by 50% and hip fracture by 25-30% by this therapy. Bisphosphonates (SERMs) increase bone density and decrease the rate of fractures. A Synthetic STEAR, tibolone was associated with a decrease in relative risk of vertebral fracture and nonvertebral fractures. All women also received 600-1200 mg of calcium citrate and 400-800 IU of Vitamin D[7].

Cardiovascular Disease

The earlier concept that estrogen replacement therapy is cardioprotective has been challenged by the negative results of randomized clinical trials in coronary heart disease. There was a significant (50%) increase in cardiovascular events in the first year on estrogen therapy. It is clear from HERS (Heart and Estrogen Progestin Replacement Study) , ERA (Estrogen Replacement and Atherosclerosis) trial and MWS (Million Women Study) results show that use of estrogen replacement for secondary prevention of cardiovascular disease is doubtful. Further, these trials suggest that current HRT regimens should be avoided in women with pre-existing coronary artery disease [8,9,10].

The largest and most influential trials are the two arms of Women's Health Initiative (WHI), set up specifically to investigate whether use of HRT reduced the incidence of coronary artery disease in otherwise healthy women. Both for coronary artery disease and venous thromboembolism ,there is some evidence that the relative risks are greater in the first year after randomization than subsequently. The increased risk of cardiovascular disease in the large randomized trial was found in the oldest women and in

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those who started HRT late after menopause began[11].

The use of HRT in order to reduce menopausal symptoms should be limited to younger postmenopausal women at low risk for cardiovascular diseases, starting in the period close to the beginning of menopause. Preliminary publication of results of WHI concluded that HRT was unsafe to use other than for short-term relief of menopausal symptoms.[8,9,10] But subsequent publications of the WHI have shown no significant increase in CHD[12]. Another follow up study shows that estradiol/dydrogesterone use of several months to a few years is not associated with a higher risk of cardiovascular event than use of other HRT.[13]

Alzheimer's Disease (AD)

Women are at a higher risk of Alzheimer's disease than men after the age of 80 to 85 years, may be because of postmenopausal depletion of endogenous estrogens and consequent loss of their neuroprotective effects. HRT might decrease the probability of developing AD. An analysis based on longitudinal Cache County Study shows that AD was less frequent in females who had taken HRT than in those who hadn't taken. The risk of AD decreased as the duration of HRT use increased (these results indicate that HRT may be effective in the primary prevention of AD) [14].

Cochrane systemic reviews analysed a total of seven trials including 351 women with AD and concluded that after two months of transdermal diestradiol treatment, a significant effect was observed for the word recall test. No other significant effects were found for other outcome measured. So the authors' conclusion was that currently HRT or ERT (estrogen replacement therapy) for cognitive improvement or maintenance is not indicated for women with AD [15]

The use of tibolone should be avoided in older women, those at high risk for stroke and those who have breast cancer or one at high risk for the disease. Tibolone had other effects similar to those of therapy combining estrogen and progestin [7].

Problems associated with Estrogen-Progestin Therapy

Venous Thromboembolism

The problem of thromboembolic disease development with HRT is a matter of concern. A study estimated that the absolute risk of deep vein thombosis among women on estrogen is about 3 per 10,000 women years. According to HERS, risk of deep vein thombosis increases by 2 to 3.5 times with estrogen and progestin therapy. Selective Estrogen Receptor Modulators (SERMs) have also been associated with increased risk of venous thromboembolism. Risk of venous thrombosis increases with age among women. Other risk factors of venous thrombosis

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include obesity, immobility, trauma and surgical procedures[16].

A cochrane systemic review assessed the effects of HRT in primary and secondary prevention of cardiovascular disease in PMN from ten randomised placebo controlled trails published in the last decade. No protective effect of HRT was seen for any of cardiovascular outcomes assessed. Rather, higher risks of venous thromboembolic events ,pulmonary embolus and stroke were found in postmenopausal women. Authors discourage the use of HRT for the only purpose of preventing cardiovascular disease and also advise against using HRT in case of other risk facts for venous thromboembolic events[16].

Endometrial Neoplasia

Abnormal progression of growth through simple hyperplasia, complex hyperplasia, atypia and early carcinoma has been associated with unopposed estrogen activity, given either continuously or in a cyclic fashion. More than thirty studies have demonstrated that the risk of endometrial cancer is increased by 8-10 times with 10 year usage[17].

The risk of endometrial carcinoma can be reduced by reduced by addition of a progestational agent to the regimen, whereas estrogen promotes the growth of endometrium, progestins inhibit this growth. However, appropriate monitoring of patients is a must during the therapy[17].

Tibolone, a synthetic steroid with estrogenic, progestogenic and androgenic properties has also been linked to an increased risk of endometrial cancer[18].

Breast Cancer

A review of epidemiologic studies on postmenopausal hormone therapy and the risk of breast cancer fails to provide definite evidence regarding this issue.

MWS and WHI reported that continuous combined HRT use was associated with an increase in the risk of breast cancer. Risk is related to the duration of use of therapy . The risk is increased by 35% with more than five years of use. Combination therapy of estrogen and progestin increases the risk more than does estrogen alone [19] . To tackle this problem, it has been suggested that the progesterone can be given directly to the uterus and estrogen systemically or by using alternative agents like tibolone to control menopausal symptoms , which is a synthetic steroid with weak estrogenic, androgenic and progestogenic activity but with few apparent ill effects on the breast[7].

The risk of breast cancer varies with the formulation and preparation of HRT. Opposed estrogens in oral form are associated with an increased risk of breast cancer which increases with use. Transdermal opposed estrogens, unopposed estrogens and tibolone do not increase the risk[20].

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The Dilemma : To Use Or Not To Use HRT ?

To use or not to use postmenopausal hormonal replacement therapy is one of the most complex and difficult healthcare decisions. HRT, was once accepted as an ideal strategy, but its use has now decreased, keeping in view the problems associated with HRT, as discussed above. In a placebo controlled randomized trial a significant improvement was seen in vasomotor symptoms , sexual function and sleep problems in women taking HRT. There were significantly fewer hot flashes and night sweats, joint and muscle aches , insomnia and vaginal dryness. In contrast, there were increases in breast tenderness and vaginal discharge. The authors concluded that the combined hormone treatment , even when initiated many years after the menopause, can improve health- related quality of life. After telling about the benefits that can be obtained from HRT and the problems associated with HRT to the patients, the decision to take HRT or not should largely be left to the patient and her care givers. She should decide whether the symptoms are sufficient to override the detrimental effects of the therapy. The advise should be given regarding the short term use of HRT [5].

The alternative therapies like Selective Estrogen Receptor Modulators (SERMs) and Selective Tissue Estrogenic Activity Regulators (STEARs) are coming into picture. Tibolone, a synthetic STEAR has been found to be efficacious in the treatment of climacteric symptoms and prevention of bone loss. LIFT i.e., Long Term Intervention on Fractures with Tibolone trial was designed as a randomized, double-blind placebo-controlled study to show the efficacy of tibolone in reducing vertebral fractures in women with osteoporosis. Tibolone (1.25 mg) daily for 3 years was associated with a 40% decrease in the relative risk of vertebral fracture. It was associated with reduced risk of non-vertebral fracture (26%), invasive breast cancer (68%) and colon cancer (69%). It was not associated with deleterious effect on coronary heart disease or venous thromboembolism However, the risk of stroke was substantial with tibolone, in women more than 70 years of age. Endometrial bleeding was more frequent than in placebo group. There was slight weight gain, breast discomfort, vaginal discharge and infection, pelvic pain and elevations in liver aminotransferase levels [7].

The use of tibolone should be avoided in older women, those at high risk for stroke and those who have breast cancer or one at high risk for the disease. Tibolone had other effects similar to those of therapy combining estrogen and progestin [7].

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CONCLUSION

Post-Menopausal problems not always need to be managed pharmacologically. Life style changes, such as increasing physical activity, smoking cessation and maintaining a healthy diet and emotional support of family may be helpful in controlling symptoms and preventing chronic disease. For some females, hormone-replacement therapy can have an important role if given for short term. Carefully assessing the risks and benefits of HRT and taking into consideration the patients requirement, rational use of HRT (Short term) can be done. These days use of alternative therapies like SERMs and STEARs is upcoming which may substitute HRT in some patients.

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