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Postmenopausal Hormone Replacement

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Hormone replacement therapy (HRT) is a treatment for the physical, emotional, and health-risk symptoms associated with menopause. HRT may include the replacement of estrogen alone - called estrogen replacement therapy (ERT) or estrogen plus a second hormone, progestin (synthetic progesterone). HRT relieves symptoms by elevating the levels of estrogen that drastically decrease at menopause.

Benefits of HRT

Hormone replacement therapy is a reasonable choice for women with severe menopausal symptoms. There are potentially three reasons for initiating hormone replacement therapy. They are: 1) to reduce the physical symptoms associated with menopause such as hot flashes and vaginal dryness; 2) treat psychological symptoms such as sleeplessness and mood swings; and 3) to reduce the risk of osteoporosis. Estrogen prevents the accelerated loss of bone associated with menopause, maintains bone density, and reduces the risk of hip fracture. The risk of vertebral fractures may be decreased by as much as 90%, depending upon when HRT is initiated.

Definite Benefits

Symptoms of Menopause

In the United States, 50% to 80% of women report menopause-related symptoms such as hot flashes ("flushes"), night sweats, vaginal dryness, sleep disturbances, mood swings, and depression.

- ERT/HRT effectively treats hot flashes, night sweats, sleep disturbances and other physical and psychological symptoms related to menopause.
- ERT/HRT is also effective in the management of symptoms related to changes in the vagina or urinary tract due to menopause-associated dryness.
- ERT/HRT therapy maintains skin thickness and elasticity, while preventing fine wrinkles. Results from a recent study suggest that the prevalence of hot flashes among women in HRT group was reduced significantly, compared with patients in placebo control group ($p < 0.0001$).¹

Osteoporosis

- An important reason to take ERT/HRT long term is for its benefit on bone. It is effective for the prevention and treatment of osteoporosis. ERT/HRT, if continued for a prolonged time, inhibits bone loss and decreases the risk of bone fractures.
- Increased physical activity and adequate intake of calcium and vitamin D may

also reduce the risk of osteoporosis-related fractures.

Areas of Uncertainty

Coronary Heart Disease

Before menopause, women have a lower risk of heart disease than men, but after menopause, a woman's risk for heart disease rises.

Risk factors for CHD in women are well documented.² HRT may be associated with a reduction in the risk of cardiovascular disease by modulating the risk factors associated with it. Estrogen has a favorable effect on cholesterol; it decreases the total cholesterol while increasing high-density lipoproteins (HDL) and decreasing low-density lipoproteins (LDL) cholesterol levels. Estrogen may also act upon the coronary arteries to prevent plaque formation and increase blood flow.³ Early observational studies have suggested a protective mechanism for HRT in CHD.⁴⁻⁵

However, recent studies have cast doubt on HRT's protective effect on the heart. The Women's Health Initiative, a primary prevention study, has not yet been formally reported. However, it has informed participants that among predominantly healthy women randomized to HRT, there was an early increased risk of cardiovascular events compared with women randomized to placebo. In the first two years of the trial, there was an excess of MI and stroke.⁶

The recent findings from the Heart and Estrogen/Progestin Replacement Study (HERS) have challenged previous observational data regarding the role of hormones in preventing subsequent cardiovascular events. The authors concluded that they could not recommend starting HRT for secondary prevention in CHD, but if a woman were already taking HRT, it would be appropriate for her to continue.⁷

In light of these new findings, HRT may actually increase the risk of cardiovascular events in women with coronary heart disease - at least in the first 1 to 2 years of use. Therefore, HRT should not be used for the express purpose of preventing heart disease. In a recent statement, the American Heart Association (AHA) has recommended that HRT should not be initiated for the secondary treatment of CHD and recommends that there is insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of stroke.⁸ Women should be evaluated for any risk factors for cardiovascular disease, such as, high blood cholesterol, high blood pressure, diabetes, and should treat them, if present.

Cholesterol -- The addition of progestin to estrogen in modern HRT attenuates the increase in HDL seen with estrogen alone. The recently reported Post-menopausal Estrogen/Progestin Interventions (PEPI) Trial, a randomized, double-blind, placebo controlled trial in 875 post-menopausal women, found that combined estrogen-progestin therapy increased HDL and decreased LDL, although the amount of the effect on HDL was greater with estrogen alone.⁹ In the Medical Research Council (MRC) trial, a randomized trial of estrogen alone (PremarinTM) or estrogen plus norgestrel (Prempack-C) in 321 women with hysterectomies, LDL cholesterol fell in both groups, whilst HDL cholesterol increased in women taking estrogen alone but not in those taking combination therapy. However, hormone-treated women had higher triglyceride levels than women on placebo in the MRC trial, this being more marked in women receiving estrogen only.¹⁰

Blood pressure -- There has been concern about the use of HRT in postmenopausal women with concomitant hypertension, and several studies have been carried out to assess the effect of HRT on blood pressure in hypertensive women. Lip et al. studied 75 hypertensive women treated with HRT for menopausal symptoms.¹¹ After a mean follow-up of 14 months in this open non-randomized study, no significant change in blood pressure was found in the women receiving HRT as estrogen/progesterone combination or estrogen only preparations. Kornhauser et al. conducted a randomized, double-blind study in postmenopausal women with mild to moderate hypertension and found no increase in blood pressure in this group after 90 days' treatment with estrogen alone or estrogen/progesterone combination,¹² although a fall in plasma renin activity and aldosterone levels in treated women was noted. Other studies on the effect of estrogen/progesterone combination HRT on blood pressure in normotensive women have shown a significant fall in diastolic blood pressure and no change in systolic blood pressure.^{13,14}

Diabetes -- Hammond et. al. in a retrospective study found that there was a significant reduction in the onset of diabetes in women treated with HRT.¹⁵ This was also found in a prospective study by Lafferty et. al. with none of the women receiving HRT developing diabetes, compared to four in the control group.¹⁶ The small numbers involved, however, do not enable one to draw any firm conclusions about the effects of HRT on the development of diabetes. Nevertheless, in the PEPI study, fasting insulin and glucose levels were slightly reduced in women assigned active treatment, suggesting that insulin resistance is decreased by HRT.⁹

Recently, in a randomized controlled trial, Manning et. al. concluded that in women with type 2 diabetes mellitus, combined continuous HRT had beneficial effects on lipoprotein concentrations and improves some markers of coagulation and glyemic control.¹⁷

Mental Dysfunction

Reports from a number of early studies suggest that cognitive dysfunction or Alzheimer's disease is less likely to develop in women who take estrogen after menopause. More recent studies have, however, failed to support this hypothesis. Studies are underway to evaluate the role, if any, of estrogen in the prevention of memory loss and cognitive decline.¹⁸ Recent data from the HERS study suggests that among women who reported hot flashes at study entry, treatment with HRT was associated with improved mental function and decreased symptoms of depression.¹

Colorectal Cancer

Studies suggest that the use of HRT reduces the risks of colorectal cancer. However, these results are inconsistent.

Side Effects and Risks of HRT

There are several potential side effects that can occur with HRT in varying frequencies. These side effects include bleeding, weight gain, breast tenderness, headaches, mood swings and skin irritation. Most side effects of HRT can be improved or corrected by making changes in the replacement treatment and/or dosage. As many as two-thirds of women who start HRT stop within 2 years. One main reason they stop is because of side effects, particularly the irregular menstrual bleeding.

Definite Risks

Endometrial Cancer

Many studies have demonstrated that the long-term use of estrogen alone increases the risk of cancer in the uterus. Addition of a sufficient dose of a progestin, which opposes the effects of estrogen on the endometrium, eliminates these risks and should be an integral part of postmenopausal hormone-replacement therapy for a woman with an intact uterus.

Venous Thromboembolism

Studies have shown that postmenopausal use of estrogen increases the risk of deep venous thromboembolism (formation of blood clots within blood vessels).⁷ Recent report suggests that there is a significant venous thrombosis amongst women on HRT compared with women on placebo (p=0.003).¹

Probable Increase in Risk

Breast Cancer

HRT may increase the risk of breast cancer particularly with long-term use. Some studies show a slightly higher risk of breast cancer for women who have undergone hormone replacement therapy for more than 10 years. There are no increased risks of breast cancer or uterine cancer when HRT is used for shorter periods of time (five years or less).

Gall Bladder Disease

Studies have reported that the risk of gallstones is increased in postmenopausal women who are taking estrogen. Also, it has been reported that women on HRT have a significant increase in biliary tract surgery.¹⁹

Estrogen and Estrogen/Progestin Combination

For a post-menopausal woman, it is suggested to start with the standard dose of either an oral estrogen or a combination of estrogen and progestin. Estrogen used by itself can increase the risk of uterine cancer. Therefore, if estrogen alone is replaced in women who have not undergone a hysterectomy, their risk is increased for uterine cancer. However, administering a progestin along with estrogen can reduce this risk.

For a woman with uterus removed, it is suggested to start with estrogen alone. Because the uterus is not present, there is no need to take progestin.

Dosage

The minimum dose of estrogen protects against osteoporosis, plus relieves menopausal symptoms. Progestin is added to estrogen to protect against uterine cancer as it stops uterine cells from dividing and causes the uterus to shed its lining. By this action, however, progestin can induce monthly menstrual bleeding. Standard minimum dose of oral estrogen for protection against osteoporosis and relieving menopausal symptoms, that is presently available, include 0.3 milligram (Premarin), 0.5 milligram (Estrace) and 0.625 milligrams (Ogen).

In a woman with an intact uterus, 2.5 to 5 mg of progestin is added to estrogen to protect against uterine cancer. It stops uterine cells from dividing and

causes the uterus to shed its lining. For many women these standard starting dosages work just fine. Many women quickly feel dramatically better as their hot flashes ease and they can get a good night's sleep. But there is no such thing as a one-size-fits-all HRT regimen.

One can choose oral estrogen and progestin in one of the two ways. Cyclic hormone treatment, which causes monthly bleeding, involves taking oral estrogen plus oral progestin for 10-14 days each month. With continuous combined hormone treatment, a combination of estrogen and progestin is given daily. This combination is available as a single tablet.

Application of an estrogen patch directly to the abdomen delivers the hormone directly to the blood through the skin. Because estrogen delivered this way bypasses the liver, it reduces some of the side effects and risks associated with hormone replacement. Use of the patch also reduces the fluctuations in estrogen levels. These fluctuations can result in some of the side effects such as migraines.

In order to reap the benefits of hormone replacement and minimize the side effects, it is suggested to customize treatment. A woman should discuss with her health care provider the problems or risks she is facing - cardiovascular risk, osteoporosis, hot flashes, vaginal dryness, mood swings or depression - and choose appropriate treatment. HRT comes in a variety of doses, regimens, and preparations designed to make women more comfortable during treatment while gaining long-term benefits.

Cost-effectiveness/Cost-Benefit

Currently there are no prospective economic evaluations available for the cost-effectiveness of HRT for the primary, as well as, secondary prevention of CHD. However, there have been some cost-effective models developed, suggesting that HRT may be effective. These studies have shown that HRT improves quality of life in women with perimenopausal symptoms and is a cost effective treatment for symptoms of the menopause. Daly et al (1993) showed that women were prepared to trade off 36% of their postmenopausal life-years to avoid severe menopausal symptoms.²⁰ Quality of life may be more important than length of life to many patients.¹ A number of economic evaluations have indicated that it may be also cost-effective therapy for prevention of cardiovascular disease and osteoporosis. However, these evaluations are based on the premise that HRT will reduce cardiovascular disease by 30-50%. Recent evidence casts doubt on the effectiveness of HRT in preventing cardiovascular disease.²¹ Due to the uncertainty surrounding the long-term effects of HRT, the cost-effectiveness estimates should be interpreted carefully.²²

Targeting HRT to women with low bone mass and who have other risk factors for fracture is likely to be more cost-effective than a strategy. It allows asymptomatic women with low fracture risk to take HRT. Screening of perimenopausal women with intact uterus with the intent of prescribing HRT for patients with low bone density is reported to be cost-effective when compared with universal treatment and when compared to no intervention when quality of life is considered.²³

Cardiac Event/s and HRT

Recently, it has been reported that there is no overall cardiovascular benefit. Some

studies indicate a pattern of early increase in risk of coronary heart disease events. Therefore, HRT for the purpose of secondary prevention of coronary heart disease is not recommended.

Alternatives to Postmenopausal HRT

Alternatives to HRT include the use of bisphosphonates and selective estrogen-receptor modulators (SERMs, such as raloxifene) for osteoporosis; statins to prevent heart disease; soy products and vitamin E to reduce mild to moderate hot flashes; and low-dose vaginal estrogen for vaginal symptoms of menopause. The health care provider needs to be informed about the use of any food supplements or 'over the counter' medications.

Some investigators believe that some of the side effects associated with HRT are due to the use of synthetic hormones and presently, studies are underway to compare the effect of natural and synthetic hormones. For example, it is important to know that the group of drugs that are referred to as progestins are not progesterone. They are compounds with altered molecules of progesterone.

Menopause does not always need to be treated with medication. Lifestyle changes, such as increased physical activity, quitting smoking, or eating healthy diet, may control these symptoms and prevent chronic diseases. Careful consideration of the risks and benefits of HRT, guided by the patient's preferences, can lead to a more appropriate use of HRT, pending the availability of more information from ongoing studies.

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