Hormone Replacement Therapy: Exploring the Options for Women

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ABSTRACT

Hormone replacement therapy involves restoring estrogen (female hormone) to body when levels are diminished. Menopause is the most common cause of low estrogen levels. During menopause ovaries (glands that produce eggs and hormones) stop producing estrogen and body no longer menstruate. Women who have had their ovaries surgically removed have decreased levels of estrogen and experience the same symptoms and physical changes associated with menopause. With a marked increase in longevity, women now spend one-third of their lives in the post–menopausal period. Therefore, they would have to cope with the post–menopausal syndrome and face the consequences. Again, women are now asking for a quality life after menopause. So, Hormone Replacement Therapy is a hot topic in this era it is no more for symptomatic management for post–menopausal syndrome, but for the total management from prophylactic to curative. This article reviews benefits, risks and various different approaches, including novel approaches available for Hormone Replacement Therapy, nowadays.

Keywords: Hormone replacement therapy, estrogen, progesterone.

INTRODUCTION

Women may experience a variety of symptoms associated with estrogen deficiency around the time of menopause [1]. These symptoms include hot flashes, fatigue, night sweats, mood changes, insomnia, myalgias, anxiety, sexual dysfunction, and other symptoms that can significantly affect daily life [2-5]. Hormone replacement therapy involves the provision of one or more estrogenic substances, with or without progesterone or progesterone–like drugs, to replace the circulating hormones that fall to low levels after the cessation of ovarian hormone production at menopause [6].

After menopause, due to reduced hormone levels, women face the above mentioned symptoms. In peri- and post menopausal women who have moderate to severe vasomotor symptoms associated with estrogen deficiency, hormone replacement therapy is beneficial [7]. The first demonstration of the effectiveness of natural oral estrogens occurred 60 years ago. The widespread use of estrogens did not occur until Dr. Robert A. Wilson’s “Feminine Foreever” was published.

BENEFITS FOR HORMONE REPLACEMENT THERAPY [8-14]

- Loss of libido also responds to estrogen replacement.
- Estrogen may considerably improve urinary symptoms like incontinence, frequency urgency, dysuria and difficulty in voiding by increasing epithelial thickness, vascularity, collagen content of connective tissue.
- Due to increased bone resorption, in post menopausal women, osteoporosis and fracture may occur. Estrogens help to increase calcitonin level, which causes inhibition of bone resorption.
- Estrogen gives its beneficial effect on lipid metabolism, and helps to combat cardiovascular diseases and atherosclerosis in menopause.
- Estrogen increase collagen content in skin and hence prevents varicose ulceration. It also reduces wrinkles in menopausal women.
- Hormone replacement therapy reduces risk of Alzheimer’s disease by reducing beta amyloid protein and cholinergic dysfunction in brain.
- Hormone replacement therapy enhances neuroplasticity, memory and cognition by regulating the synaptic neurotransmission.
- Onset of Parkinson’s disease is delayed by hormone replacement therapy due to its action on dopaminergic system in midbrain.
- Besides, the above mentioned benefit, estrogen prevents tooth loss and periodontal disease, decrease risk of fatal colon cancer, improve glycemic control in diabetic women, reduces cataract and nuclear sclerosis.

HORMONES USED FOR HRT

Estrogen

Almost every postmenopausal woman is on some sort of estrogen replacement therapy. In our body three different kinds of estrogen are
produced. These are: Estradiol, the primary estrogen produced during your reproductive years; Estrone, the primary estrogen produced during your menopausal years; estriol, the weakest form of estrogen, primarily available during pregnancy when it is produced by placenta. Tablets containing conjugated Equine Estrogen are one of the most prescribed estrogen formulations [15].

**Progestrone**

Estrogen may alone increase a women’s risk of endometrial cancer. Because of this, most health care providers will advice that progestrone should be taken to prevent endometrial cancer. However, women who have had their uterus removed need not worry about endometrial cancer. Progesterone is added to estrogen therapy at least 12 days a month progestins commonly used are medroxyprogesterone, norethindrone, and norgestimate [16].

**VARIOUS FORMULATIONS USED IN HORMONE REPLACEMENT THERAPY**

Although various types of hormone replacement therapies have been established, the route of administration is one way to improve benefits, decrease the risks and side effects and improve compliance. Individual variations in response to different dosage forms increase the importance of having a choice of dosage forms to optimize potential outcomes.

**Oral tablets and capsules**

Oral estrogens may be used to treat vasomotor symptoms; e.g. Estrace®, Premarin®, and Prempro™. The dosage of oral estrogens often begins with a low daily dose such as 0.3mg or 0.625 mg of CEE (Conjugated equine estrogen). Tablets are easy to take, comparatively cheap, raises levels of HDL but need to be taken everyday [17-19].

**Gels**

Gels are totally invisible with excellent cosmetic properties. Gels are used for the treatment of moderate to severe hot flashes and moderate to severe dryness, itching, and burning in and around vagina. This technology consists of a hydro alcoholic gel containing a combination of permeation enhancer. Gels are applied once a day to arm from wrist to shoulder; e.g. Estrogel®. Estradiol gel contains 0.06% Estradiol in an absorptive hydro alcoholic gel base formulated to provide a control release of the active ingredient. Low dose of transdermal estrogen begin at 0.0375 mg per day or 0.05mg per day. Percutaneous administration of Estradiol gel produces plasma concentrations of Estradiol and Estrone that are similar to those observed in the follicular phase of the ovulatory cycle. The formulation does not cause irritation or occlusion of the skin after the application. Gels give control release of drug. Moreover, gel completely disappears within two to three minutes after applications, leaving no residues on skin avoiding greasy feeling. Improved patient compliance can be anticipated, owing to the ease of application and cosmetic elegance [20-21].

**Lotions**

Lotions are used for treating moderate to severe symptoms of hot flashes and night sweats associated with menopause. Women apply white lotion like emulsion to their legs on daily basis; e.g. Estrasorb™ (Estradiol topical) [22].

**Vaginal Cream**

Creams are generally used to treat vaginal symptoms of menopause. Most creams must be applied to twice a day; e.g. Estrace®, Ogen®, Premarin®. Creams have dosage flexibility. Consistency of creams can be changed depending on the absorption required and site of application. Creams can be made preservative free to minimize patient allergies and sensitivities [23].

**Vaginal Ring**

Vaginal ring contains a mixture of crystalline 17b-estradioland and an inert polymer. Vaginal rings are used for the treatment of urogenital complaints related to menopause, including vaginal dryness, urinary urgency, painful intercourse and painful urination. These are also used to treat severe hot flashes, night sweats and vaginal dryness. Examples include Femring and Estring. The ring is a small piece of circular plastic silicon that is inserted into the vagina like a diaphragm, where it releases a steady dose of estrogen for three months, at which point it is replaced. Systemic absorption through vaginal epithelium depends on the surface area of ring [24].

**Patches**

Patches are rate control systems for adminstering plasma Estradiol through intact skin. Patches are applied for a variety of menopause symptoms, including hot flashes, vaginal symptoms and osteoporosis. Examples include Alora®, Climara®, Estraderm®, Menostar™, and Vivelle® etc. These are applied to abdomen or upper buttock. They have varied dosing with some are applied once a week and others twice weekly. These may cause skin irritation and are expensive, otherwise patches are convenient, easily reversible, and give more natural delivery of hormone. These days newer patches are coming in market that do not contain alcohol as they cause fewer skin reactions but deliver estrogen as efficiently as originals [25-26].

**Vaginal Tablets**

Vaginal tablets are generally used for relief of vaginal symptoms like vaginal atrophy, e.g. Vagifem. These tablets have to be inserted into the vagina via a disposable applicator. These tablets are to be taken one tablet daily for first two weeks, but afterwards one tablet twice a week will serve the purpose [27-28].

**Implants**

Crystalline Estradiol implants are placed subcutaneously in the abdomen or buttock. Implants provide stable circulating levels of Estradiol for a period of 4-12 months. Dosing in implants is not easily adjusted and endometrium stimulation is possible even after discontinuation of therapy [29].

Besides, the above mentioned dosage forms, nasal sprays, injections, implants, suppositories, hormones impregnated intrauterine devices etc. are now available in the market for hormone replacement therapy.

**HRT- RISKS AND CONCERNS**

**Endometrial risk**

Continuous use of estrogen can cause endometrial hyperplasia, leading to endometrial carcinoma. No such changes were observed in women taking estrogen plus continuous cycle medroxyprogesterone acetate or cyclic medroxyprogesterone. Cyclic progesterone therapy (more than 12 days per month) is as effective as continuous low-dose progesterone therapy, and various progestins (medroxyprogesterone acetate, micronized progesterone) are equally efficacious in reducing the risk of endometrial hyperplasia [30-32].

**Breast neoplasia**
A serious concern for women taking long term hormone replacement therapy is the reported increased risk of breast cancer. Several epidemiological studies have reported an increased risk of breast cancer, and risk is higher with estrogen-progestogen combinations than with estrogen alone. There was an increased risk of breast cancer only in women who had used hormone replacement therapy for five or more years; the risk for each year of added use was the same as the risk for each year of delayed menopause-providing internal consistency for an estrogen-breast cancer association. One large observational study of over 5000 women found that unopposed estrogen use did not increase breast cancer risk until 15 or more years on therapy. In contrast, breast cancer risk increased about 10 % per five years of hormone replacement therapy use [33-34].

**Ovarian Neoplasma**

Unopposed estrogen therapy may cause endometrial tumor. A recent study reported an increased risk of ovarian cancer in women taking postmenopausal estrogen replacement therapy for more than 10 years but no risk of ovarian cancer among users of continuous combined hormone replacement therapy [35].

**Venous thromboembolic disease**

Studies generally show an increased risk of deep vein thrombosis and pulmonary embolus in women taking hormone replacement therapy. The absolute risk in current users is small, with estimates of 16 and 23 excess cases per 100,000 women a year for all venous thromboembolic and 6 per 10,000 a year for pulmonary embolism. Women taking hormone replacement therapy have twice the risk of venous thromboembolism compared with non users. The risks of venous thromboembolism with hormone replacement therapy are likely to be greater in women with predisposing factors such as a family history of thromboembolic disease, severe varicose veins, obesity, surgery, prolonged bed rest and age is an important risk factor [36].

**CONCLUSION**

The goals of the therapeutic approach is not to increase further longevity but to correct symptoms and prevent diseases related to this decline in hormonal secretion of the menopausal ovary, in order to improve the quality of life of aging women and their families as life expectancy is increasing anyway. The benefits of estrogen administration must be balanced with potential risks based on the best available evidence. A decision analysis tailored to the individual is more appropriate than is a population-based approach to treatment. The patient who desires treatment should be able to make an informed decision regarding the risk and benefits. Also, as risks associated vary due to type of estrogen delivery system. Therefore, depending on the symptoms and patient acceptance, cost of therapy, ease of use of therapy, and absence of unwanted side effects, appropriate delivery system can be chosen.

**FUTURE POTENTIAL**

The 50 or so different hormone replacement therapy formulations that are currently licensed in the United Kingdom offer many options to menopausal women. These range from oral and transdermal products to those administered intranasal and vaginally. Besides these, various herbal formulations are also available in market for hormone replacement therapy in which Soy, Red Clover, GardenSage, Chastevery and Valerian are used. So, more efforts can be put on researching new technologies and combinations which help in reducing risks and side effects related to hormone replacement therapy.

**REFERENCES**

25. Simon, J., Rogers, R., Ragavan, V., Ibarra, de Palacios, P. Menopausal women prefer patches to pills for hormone replacement therapy. Presented at: 10th World Congress on Menopause; June 10-14, Berlin, Germany, 2002.

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