Menopause & hormone replacement therapy
Parveen T, Hussain MA

Reproductive age of women starts and ends with two distinct events, menarche i.e. starting of menstruation and menopause i.e. complete cessation of menstruation. These two events are universal and associated with social, medical and demographic significance. At menarche a girl is magnified to her womanhood while at menopause a complete woman feels inferior as she feels that one of her qualities of womanhood has disappeared, so she may be neglected in her family. In addition to this psychological upset, women also experience very distressing physical problems which result from acute decline of ovarian production of estrogen, the "Estrogen Withdrawal Syndrome". With the increase in life expectancy, about one-third of a woman's life is now spent in the post-menopausal era. So this crucial part of the life of women needs sympathetic and scientific approach.

Natural menopause is recognized retrospectively after 12 consecutive months of amenorrhea when there is no other obvious pathological and physiological cause. The endocrine activity of the ovary is the production of estrogens and progesterone which is ceased in menopause. Deficiency of the female hormones particularly estrogen has a profound effect on the quality of the health of the menopausal women. The sequelae of ovarian failure in menopause may be divided into short-term and long-term

The short term sequelae are

Vasomotor symptoms
• Hot flushes
• Night sweats
• Palpitation
• Insomnia
• Headache

Mood disorders
• Depression
• Anxiety
• Irritability
• Mood swings
• Lethargy, etc.

Urogenital
• Vaginal dryness
• Dyspareunia
• Urethral syndrome

The long-term sequelae are

• Osteoporosis
• Cardiovascular disease

In Bangladesh a study at the 'Thana, Union & Village level' showed that 65% of the postmenopausal women found to have burning sensation of limbs, vertigo and headache. 44.2% had complained of insomnia.

As most of these distressing symptoms are attributed to estrogen deficiency, Hormone Replacement therapy (HRT) i.e. replacement of these hormones particularly estrogen appears as the solution in most cases.

1. Dr. Tabassum Parveen, MBBS, FCPS (Obs & Gynae) Assistant Professor, Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU)
2. Prof. M Anwar Hussain, MBBS, FCPS (BD), FRCOG (London), FICS Professor, Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU)
Estrogen is indeed the closest thing in modern medicine to an elixir of youth—a drug that slows the ravages of time for women.

The era of effective estrogen therapy began with the crystallization and identification of oestradiol by a co-worker of Ernst Schering. In 1934 Schering started marketing of orally active steroid, Ethinyl oestradiol. In 1966 American gynaecologist Mr. Robert A. Wilson in the book 'Feminine Forever' gave the exciting notes. He wrote 'for the first time in history of woman may share the promise of tomorrow as biological equals of men... . Thanks to HRT, they look forward to prolonged well-being and extended youth.'

Hormones that are used in HRT are estrogen, key part and active component to control the menopausal symptoms and progestogens which are normally used in combination with estrogen to prevent the unopposed influence of oestrogen on body particularly on endometrium of uterus, where it can cause endometrial carcinoma.

Estrogen preparations that are available are of two forms:

**Synthetic estrogens**
like ethynyl oestradiol, mestranol. These are largely replaced by natural oestrogens because of their greater metabolic impact.

**Natural estrogens**
These are of three types. Oestradiol, Oestrone and Oestriol.

Natural estrogens are chemically synthesized from Soya Beans or yams. Conjugated equine oestrogens are also considered as natural where 50-65% is oestrone and rest is derived from oestrogens.

In Estrogen-Progestogen combination of HRT, progesterone preparations are usually synthetic and used to reduce the risk of endometrial hyperplasia and malignancy.

HRT preparations that are available can be divided into two general categories.

**Oral preparations**
Estrogen only, Estrogen-Progesterone combination & Tibolone.

**Parenteral preparation**

**Transdermal**
Two transdermal systems are available - patch and jell. These are self adhesive and consist of mainly oestradiol which delivers this hormone over a period of 3-4 days.

**Subcutaneous implants**
These are pellets of fused, crystalline oestradiol, needs surgical procedure to implant, release the hormone over a period of 4-8 months.

**Vaginal & nasal preparation**
Estrogen and progesterone are also absorbed through vaginal and nasal mucosa leading to the development of vaginal rings and nasal sprays.

**Creams or jells**
Estrogen are also available for topical use to prevent atrophic vaginitis and dyspareunia.

The benefits of HRT for the relief of acute climacteric symptoms are well recognized. Unopposed estrogen may be effective for reducing the awaking episodes that are associated with sleep disruption. The vasomotor symptoms of menopause like hot flushes, night sweats, headache and palpitations are readily treatable by small dose of estrogen, whatever is the route of
administration. But to alleviate the psychological complaints associated with menopause like depression, anxiety, loss of energy, loss of libido and irritability, the role of HRT is not well established.

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. Postmenopausal osteoporosis is a major public health problem. Estrogen deficiency is a key factor in the pathogenesis of postmenopausal osteoporosis. Among the several types therapeutic intervention in osteoporosis, HRT is considered as the gold standard for preventing post-menopausal osteoporotic fractures. However oestrogenic effect on bone is dose-dependent. For oral therapy, studies have demonstrated that doses of 0.625 mg of conjugated equine oestrogen and 2 mg of micronised oestradiol prevent postmenopausal bone loss. Perectaneous 17 beta-estradiol prevents skeletal bone loss as effectively as oral HRT. Although the greatest benefits from HRT in terms of bone sparing effects can be obtained shortly after the menopause, evidence showed that HRT prevents bone loss in all stages of postmenopausal life. However, estrogen therapy must be long-term, possibly lifelong, to have any lasting impact on bone health.

A study to investigate the effect of conventional and high doses of estrogen and bisphosponates or SERMs on the degree of mineralization of bone (DMB) was carried out in France. Study showed that estrogen therapy was associated with an increased degree of mineralization of bone induced by a secondary mineralization, similar to that observed with other antiresorptive agents. However, this increase was about two-fold lower than that observed after alendronate therapy (10 mg/day/3 years).

The women’s Health Initiative study (WHI) showed of reduction of colo-rectal cancer among HRT users from 16 to 10 cases.

However the most spectacular findings of HRT use of this century was regarding its effect on cardio-vascular system. For many years it was believed that estrogen replacement after menopause gives protection from cardio-vascular disease by reducing low-density lipoprotein (LDL) and increasing high-density lipoprotein (HDL). The large trial 'Heart and Estrogen Replacement Study (HERS)' compared the effects of combination of the hormones estrogen and progesterone against a placebo in 2, 763 women with heart disease. At the end of five years, there were no differences in heart attack rates between the two groups. What's more, hormone therapy appeared to increase the rate of cardio-vascular problems during the first year of use. HERS II trial, a follow up study of HERS I, also confirmed the initial findings of HERS I trial, the report of which was published in the July 2002 issue of the Journal of the American Medical Association (JAMA).

The main risk to the use of HRT is development of breast cancer. Numerous studies and meta-analyses have shown that HRT increases the risk of developing breast cancer, estimated to be 2.3% for each year of use. The key findings of the Women's Health Initiative study (WHI) after five years in 10,000 women breast cancer was found to be increased from 30 to 38 cases (did not appear in the first four years of use). A Danish cohort study using longitudinal data from the population-based prescription database of the country of north Jutland, Denmark, and the Danish Cancer registry, was done to find the risk of developing
breast cancer in relation to HRT in a cohort of 78,380 women aged 40-67 years from 1989 to 2002. A total of 1462 cases of breast cancer were identified during a mean follow-up of 10 years. Use of HRT did not increase the risk of breast cancer in women aged 40-49 years. Restricting the cohort to 48,812 women aged 50 years or more at entry, of whom 15,631 were HRT user, an increased risk of breast cancer was found associated with current use of HRT (relative risk 1.61, 65% confidence interval 1.38-1.88). The risk increased with increasing duration of use and decreased with time since last HRT prescription, reaching unity after 5 years. No material risk difference was observed among the various HRT regimens. This population-based cohort study provides further confirmation that HRT increases the risk of developing breast cancer in women aged 50 years or more.

So HRT is not recommended for routine use in menopause. It should be used for as short a time as possible with lowest effective dose. Researches are continuing on. The results of such researches will hopefully give a clear or at least clearer picture of the benefits and risks of hormone replacement therapy in near future.

References
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