It is important to know that these menopausal symptoms may have their onset prior to actual cessation of menses, since estrogen levels fall progressively in perimenopausal and also changes in skin and core temperature and skin resistance, precede LH and FSH secretory rises by just a few minutes.

**Osteoporosis**

Bone is metabolically active tissue that is being constantly remodeled. Old bone is reabsorbed by osteoclasts, and new bone is deposited by osteoblasts. Whether new bone loss or accretion occurs depends on balance between the activities of these two kinds of cells. Osteoporosis or diffused osteopenia, is a condition of reduced bone mass resulting from a relatively long period of negative imbalance in remodeling process. A rate of demineralization from 2 to 5% in a year occurs at menopause and has been documented with other cause of severe estrogen deficiency. During the first five years of menopause calcium is primarily lost from trabecular bone e.g. vertebrae, whereas loss of calcium occurs equally from trabecular and cortical bone (hip and long bones) in later stages and eventually fractures may occur. Crush fractures of vertebral body predominate causing back pain, loss of height and stooped posture (dowager’s hump). Osteoporosis is most common in caucasian and Asian than in African and American women. Studies have shown that at the age of 70 years, the bone mass lost in the woman is 25%. One in four osteoporotic fractures occur by mid sixties, HRT if given for 5 years reduces osteoporotic fracture by 35%.

**Known risk factors for osteoporosis are estrogen deficiency states, cigarette smoking, family history, fine body structure (i.e, low peak bone mass at maturity) prolonged bed rest, sedentary life style, alcohol abuse, diabetes mellitus and chronic gluco-corticoid therapy.**

Bone loss occurs with aging.
menopause, deficiency of minerals like calcium and vitamin D and can occur as a result of medications, diseases and surgical procedures like oophorectomy. The most common endocrine disorders that leads to bone loss includes abnormalities in sex hormones, thyroid hormones, parathyroid hormones, and adrenal steroids. BMD (Bone Mineral Density) detects osteoporosis before fracture occurs, predicts fracture chances in future. The hip BMD is best predictor of hip fractures and is recommended to be done first.

Osteoporosis is better prevented than treated. Goal of prevention is to achieve a peak bone mass genetically possible prior to skeletal maturity, which can be accomplished by:

i) Proper nutrition, sufficient weight bearing activity, minimising of risk factors like smoking, alcohol abuse and immobilization.
ii) By continuing these beneficial habits through adulthood to maintain bone mass and
iii) By using ERT in women at risk.

For prevention (1500 mgs calcium and 400 IU vitamin D per day) decreases bone loss associated with osteoporosis. Regular exercise, good diet, avoiding smoking is important.

Psychological symptoms

The psychological response to menopause may range from little or none to profound alteration of affect and personality. Symptoms vary from minor irritability and emotional liability, mood swings, dementia to severe depression and withdrawal from usual activities. Sexuality also commonly affected, with women reporting an increase in libido while others show reduction in sexual interest, usually associated with loss of attractiveness and femininity.

Genital and Breast Atrophy

The female reproductive organs undergo striking changes at the time of the menopause. Pubic hair becomes sparse and lank, the labia majora lose their fullness and the skin and mucous membranes of the genitalia become thin and dry. The vaginal pH becomes more alkaline as glandular secretion of glycosgen is lost. This change and the mucosal atrophy may result in a chronic vaginitis with itching, discharge, and local tenderness. Many women report decreased lubrication at intercourse and complain of dyspareunia.

The cervix uterus and fallopian tubes also shrink. Estrogen deprivation is implicated in the relaxation of pelvic ligaments and muscles, which may result in uterine or bladder prolapse and contributes to stress incontinence. At the same time glandular breast tissue involutes, and the breasts become shrunken and pendulous. There is a decrease in the erectile response of the nipple.

Estrogen Replacement Therapy and Hormone Replacement Therapy will be studied under following headings:

i) WHI (Women’s Health Initiative) controversy.
ii) Risk and benefits of estrogen / hormonal replacement therapy.
iii) How HRT is taken.
iv) Various types of HRT therapies and non-HRT options.
v) Does duration of hormone therapy affect breast cancer risk.
vi) What kind of research is under way.

WHI controversy:

WHI was established in 1991 by Govt. It enrolled 17,000 post-menopausal women during the period 1993-1998 of age group 50-79 years with an intact uterus. The study showed that risk out weighs the benefits of using combined drugs as replacement therapy. It showed increase in breast cancer, heart attacks, strokes and blood clots. These risks out weighing the drugs actual benefits. A small decrease in hip fracture and decrease in colorectal cancers. Trial was stopped because of risk benefit balance, as the global indicator of overall risks was unfavourable and breast cancer crossed safety limits.

As WHI study among 10,000 postmenopausal women with a uterus (as opposed to those who have had hystrectomy) who are taking estrogens and progestin

- Seven more will have heart attacks.
- Eight more will have invasive breast cancer.
- Eight more will have stroke.
- Eighteen more will have blood clots.

Than with a similar group of 10000 women not taking these hormones.

- WHI has however continued studies with the estrogen only portion of the therapy.
- And studies of women on estrogen replacement therapy who have had hystrectomy.

Coronary Heart Disease:

WHI has shown that continuous combined HRT should not be used for primary prevention of coronary heart disease in a healthy population of largely asymptomatic women spanning three decades after menopause. In fact combined HRT was associated with small but significant risk of adverse cardiovascular events. Deaths due to cardiac disease were equivalent to 15 and 13 per 10000 women – years estrogen – progestin respectively.

At present in absence of any cardiovascular protection from continuous combined HRT in clinical trials, primary prevention of coronary heart disease depends on healthy lifestyle choices (smoking cessation, exercise, weight control) and pharmaceutical agents with established value for prevention or treatment of cardiovascular disease such as lipid lowering agents and anti-hypertensive agents.

Breast Cancer

WHI has shown in its study that breast cancer risk did not significantly increase during the continuous use of combined HRT for up to 4 years. The risk was statistically significantly elevated after 5 years of use.

Dr. Barnabei (Associate Professor of Obst. And Gynae. At MCW and Director of Division of Obst. And Gynae.) says that Scientists have shown progestin can act to influence breast growth and development, while reducing risk of uterine cancer. Article in January 26th, year 2000 in Journal of American Medical Association reported increase risk of breast cancer in women on estrogen and progestin than in women who took estrogen alone.

Osteoporotic fractures:

WHI study confirmed reduction in osteoporotic fracture in women on combined HRT and can anticipate protection against it.

What Patient should know according to WHI Director Dr. Rossouw:

If the combination hormones is taken for short-term
relief of vasomotor and other symptoms it may be reasonable to continue it for 2 to 3 years, since the benefit likely to outweigh risks. Long-term use for disease prevention should be re-evaluated considering the multiple adverse effects noted in WHI study. Evaluation in terms of vaginal bleeding of unknown cause, history of endometrial cancer, suspected breast cancer or history of breast cancer, chronic liver disease such as cirrhosis or history of blood clots

One can stop HRT any time, without major consequences, except for return of menopausal symptoms.

**Conclusion of WHI study:**

Although more than 2/3 of the women in WHI study were over 60 years, more than in any previous study and more than the sum of patients in nearly all previous randomized control trials. It was seen that estrogens for younger age group (40 to 45 years) gives protection and prevents plaque formation. Bad beyond more than 60 years because estrogens known to increase metalloproteinases and gelatinolytic activities in coronary arteries displaces atherosclerotic plaques already formed and so increases adverse cardiovascular events.

**How HRT is taken:**

- 0.625 mg of Conjugated estrogen premarin is taken each day, unless you have had a hystrectomy, progestin is also taken to decrease risk of uterine cancer. Estrogen / progestin are available in both pill and patch form.
- Transdermal patch (estradiol 100μg per 24 hours).
- HRT daily dose gives plasma level of 200 pg/l.

**Hormonal therapy is given in many ways:**

- Continuous cyclic therapy.
- Continuous combined therapy.
  - (Fixed Continuous dose of estrogen and progestin) – progestin 5 to 10 mg medroxy-progesterone for 10 to 14 days of each cycle.
  - Long cycle therapy.
  - (3 months continuous estrogen and progestrone)–progesterone for last 12 days.

American college of Obst. And Gynaec. in April 2003 showed that continuous estrogen therapy advocated because no proven benefits to drug free interval seen.

Estrogen to be started with low dose at three monthly interval. If fails to control symptoms, change the type of estrogen, progestrone and also way of delivery.

**Initiating and Planning of HRT therapy:**

- Perimenopausal.
- Postmenopausal

For therapeutic purposes HRT can be started at any time provided the symptoms warrant treatment and adequate pre-therapy assessment has been performed. For prophylaxis, HRT is generally started after 6 to 12 months of ammenorrhea, when diagnosis of menopause is certain.

However, if hormone therapy has not been started at that time, it can be started in elderly geriatric age group even in 7th and 8th decade, but to be started with a very low dose of 0.325 mg than gradually increased to 0.625 mg after some months if necessary.

**For how long therapy to be given:**

**Therapeutic:** The patient tend to discontinue HRT after acute symptoms disappear. However, the hormone should be gradually withdrawn, otherwise symptoms will recur on abrupt withdrawal.

Counseling is of paramount importance to encourage patients to continue with longer term use for prophylactic purposes. Studies indicate that BMD density declines after discontinuation of estrogens and approaches level of non-users, therefore it could be continued indefinitely, or other osteoprotective agents initiated.

Literature reports use of HRT as long as 20 years and more. Retarded therapy may be considered of using one HRT type for few years followed by other in case of longterm use.

In order to obtain maximum protection from osteoporosis women should start ERT at menopause. Studies suggest that 5 years may be adequate. Females without any menopausal symptoms and without risk factors for osteoporosis or heart disease may start HRT after 60 years and will gain similar osteoprotection compared to those in whom HRT is started at menopause.

**Which therapies?**

In cyclic estrogen and progestogen regimen the progestogen must be given for a minimum of 12 days. In any case there is no place for progestogen therapy of less than 10 days duration.

In long cycle therapy i.e, periods only once in three months or 4 times a year, progestogen must be prescribed for a minimum duration of 2 weeks and the dose of medroxyprogesterone acetate must be high i.e, 20 mg daily.

**Benefits of HRT:**

- Prevents osteoporosis.
- Symptom relief from hot flushes, palpitation and vaginal symptoms.
- Decreased frequency of repeated vaginal infections.
- Decreased frequency of recurrent urinary infections.
- Less musculoskeletal symptoms of aches and pains and possibly sarcopenia (or muscle wasting).
- Less menopause associated mood swings, anxiety spells, depression.
- Decreased risks of colon cancer.
- Better verbal memory, vigilence, reasoning, motor speed and cognitive brain function in symptomatic women.
- Positive benefits regards Alzheimers disease.
- Better skin, better hair.
- Long term ophthalmic benefits.
- Long term dental benefits.

**Risk Factors/ Disadvantages of HRT:**

They include breast cancer VTE, stroke, potentiation of pre existing breast cancer, increased risk of gall stones, depression, headache, premenstrual syndrome, breast tenderness, skin irritation, weight gain, menstrual bleeding. Because of substantial risk with prolonged use, a SERM, more affective with out side effects is found in EVISTA (tibolone) ,is considered as an alternative to HRT replacement therapy for women concerned about breast cancer, is
approved in 19 European countries for treatment of postmenopausal symptoms and preventing osteoporosis. It is given without progesterone.

**Contraindications for HRT:**
- Active endometrial and hormone dependent cancer.
- Active breast cancer.
- Thromboembolic disease.
- Vascular thrombosis and dependent venous thrombosis.
- Suspected pregnancy or abnormal vaginal bleeding.
- Benign breast disease have increased risk of breast cancer after 10 years of HRT.
- Family history of premenopausal carcinoma of breast.
- Fibroids which may enlarge with HRT.

**Alternative therapies:**
- SERMS: SERMS and Biphosphonates may be better alternative to estrogen replacement therapy for osteoporosis prevention in women with increased risk of breast or uterine cancer or in those women who are not willing to take estrogen replacement therapy. Studies have shown the beneficial effect of SERMS on osteoporosis prevention despite late initiation i.e. after 60 years. SERMS have the advantage of no effect on endometrium and potential beneficial effect on carcinoma breast (also called designer drug).

**Tibolone:** Tibolone is a synthetic steroid compound which has estrogenic, progestogenic and androgenic properties. It is considered more effective with least side effects and used as an alternative to conventional HRT. Replacement therapy for women concerned about breast cancer and is approved in 19 European countries for treatment of postmenopausal symptoms and preventing osteoporosis. It is given without progestrone. After oral administration, it is rapidly absorbed and metabolized into three active metabolites. It is used in dosage of 2.5 mg orally daily.

- Action on breast: Tibolone displays a progestin profile or anti-estrogrenic action in breast cells with favourable effects as far as breast tumorigenesis is concerned.
- Action on endometrium: Tibolone induces endometrial atrophy, on the lower genital tract both karyopyknotic index and maturation index improve in women who are on tibolone, thus reversing the vaginal atrophy that takes place after menopause, whilst maintaining an inactive endometrium.
- Action on bone: Tibolone has an estrogenic effect on bone of inhibiting bone resorption by reducing osteoclastic activity, BMD has shown to increase both at the lumbar spine and upper femur. This has been observed even with half the conventional dose, i.e. 1.25 mg instead of 2.5mg.
- Action on lipids: It decrease triglycerides, total cholesterol and lipoprotein (a) levels. However, it lowers HDL which is not a beneficial effect.
- Vasomotor symptoms: Tibolone is effective in reducing episodes of flushing and sweating better than conventional HRT.
- Mood and Libido: The estrogenic effect on the vagina decreases vaginal dryness and dyspareunia.
- Other effects: Tibolone has been found to mitigate the menopause related decline in muscle strength.

**Comparison with Conventional HRT:**
Tibolone has been compared with continuous combined HRT in several trials. However, tibolone causes fewer bleeding or spotting episodes and also fewer drop out rates due to bleeding and breast tenderness.

- Tibolone has also been shown to increase BMD similar to that of conventional HRT.
- The improvement in mood and libido is superior with tibolone.
- Estrogen stimulates the endometrium, where as tibolone does not, but instead causes atrophy, so there are less episodes of bleeding and spotting with later.
- Tibolone does not cause any stimulation of breast issue and may in fact reduce the incidence of breast cancer. Estrogen on the other hand stimulates breast tissue with an increase risk of breast cancer after long term therapy. Also tibolone does not increase mammographic density of the breast, which is continuous with combined HRT, thus making follow up difficult in patients on long term continuous combined HRT.
- Tibolone causes a reduction in triglycerides and total cholesterol. However, it reduces HDL levels in comparison with estrogens, which increases HDL.

**Tibolone in Indian context:**
- It is more expensive than conventional HRT.
- Women in India are particularly concerned about irregular bleeding and spotting, which is not a major issue with tibolone after the initial 3 to 6 months.
- In India where mammography is not easily available and is expensive, it may be better to use a drug where experimental evidence suggest that it does not increase risk of breast cancer.
- Hypertriglyceridaemia is the commonest lipid profile abnormality seen in Indian women along with increased Lp(a) levels. Tibolone definitely reduces the triglyceride and Lp(a) levels.

**Advantages of Tibolone:**
- Tibolone is better used in patients with family history of breast cancer or treated cases on breast cancer, or who have been on conventional HRT for 5 to 10 years.
It causes endometrial atrophy, so no irregular bleeding or spotting as compared to HRT.
For the control of vasomotor symptoms associated with GnRH analogs for treatment of endometriosis and fibroids.
Superior to conventional HRT for mood and libido improvement.
Increases BMD, decreases cholesterol and triglycerides similar to conventional HRT.
Does not increase mammographic density of breast, which is continuous with combined HRT (so follow up becomes easier with tibolone).

Disadvantages / side effects:
The main disadvantage with tibolone are reduction of HDL levels and its high cost.
Side effects include nausea in some women on initiation of therapy, but reduces in a few weeks.
Break through bleeding may also occur where patients need counseling in the first three months of treatment.
Breast tenderness which may be transitory.
Weight gain in some women.
Rarely increase in hair growth because of androgenic effect.

Non HRT modalities:
Keeping body weight under control, no smoking, avoiding alcohol, keeping cholesterol level and blood pressure under control, bisphosphonates (fosamax) helps against osteoporosis, another EVISTA (raloxifene HCL) belonging to SERMS group of drugs also protects against osteoporosis, lowers total cholesterol and prevents breast cancer.
Last but not the least diet rich in micronutrients, multivitamins and phytoestrogens, bisphosphonates and calcium, calcitonin and exercise are important non-hormonal modalities and life style factors that provide protection against osteoporosis and cardiovascular disease. They additionally help in boosting the confidence of these elderly women and improving the quality of life.

Herbal remedies:
Some women have become doubtful about HRT. Many have grown interested in herbal remedies.
There are two ways through which plants exhibit estrogenic activity in humans.
- By acting as selective estrogen receptor modulators (natural SERMS) e.g., Phytoestrogens.
- By acting as selective estrogen enzyme modulators (SEEMS) e.g., Saponins and Tanins.

Common Indian dietary sources of phytoestrogens are as follows:
- Isoflavonoids
- Bengal gram
- Chick peas
- Cherries
- Pareley
- Apples
- Mung beans
- Whole grains
- Soya
- Common Western herbs used in menopause:
  - a) Balm (Melissa Officinalis)
  - b) Black Cohosh (Cimicifuga recemosa): A very good source of estrogen and progesterone and very popular in the West.
  - c) YAMS: A protein similar to progesterone hormone, but our body lacks the enzyme needed to convert it.

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- Whole grains
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Commercially available Indian herbs for use in menopausal symptoms:
- Amaliki (Emblica officinalis), Anant Mood (Hemidesmus indicus), Arjuna (Terminalia arjuna), Ashoka (Saraca indica).

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Further Reading
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