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REVIEW ARTICLE

Menopause—Nonhormonal Approach: What's New?

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ABSTRACT

Like birth, menarche, puberty, pregnancy/delivery, menopause is also a very important natural biological event in any woman's life. Practically it's the time when a woman can enjoy life more freely with other responsibilities. As with increased life expectancy about one third of life span has to be spent without menstruation. For so long period a woman can not afford estrogen replacement especially because of its side effects and complications. That's why we have to search for better and safer options.

Keywords: Menopause, Hormone replacement therapy, Osteoporosis, Phytoestrogens, SERM.

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INTRODUCTION

The term menopause owes its genesis to two Greek words—meno means 'month' and pause means to 'halt'.[1] Menopause simply means the end of menstruation, the time when the ovaries can no longer produce the secreting female hormones. Due to increased life expectancy, specially affluent society, about one-third of life span has to be spent during the period of estrogen deprivation stage with long-term symptomatic and metabolic complications.[2,3] Although menopause is a natural biological experience like puberty, menstruation and birth. Fortunately, vasomotor disturbances, urogenital symptoms, osteoporosis and the adverse effect on lipid metabolism can now be prevented or treated and cardiovascular problems averted by well monitored and sustained hormone replacement therapy along with counseling to ensure compliance.

Etiology and Predisposing Factors

Menopause and climacteric are primarily due to aging of the ovaries which begins even before birth (20 weeks) in the form of atresia and continues throughout life (atresia and ovulation).[4] Age of menopause does not depends upon age of menarche, type of menstrual cycle, age of marriage, number of parity and abortions, climate, environment, smoking, occupation and use of various contraceptives including hormones.

Factor Governing Age of Menopause

Mainly are geographical, racial, nutritional and familial and genetic.[3] With increasing age, there is a progressive depletion of the number of follicles in the ovaries and those remain show an increasing resistance to stimulation by gonadotropins.

Endocrinal Changes

First change in ovarian function is failure in ovulation or absent or deficient corpus luteum formation that's why the first hormone to become deficient intermittently is progesterone. While reduction of plasma estradiol in premenopausal women stimulates negative feedback mechanism of the hypothalamus and pituitary causing raised follicle stimulating hormone (FSH) which is the most characteristic endocrinal change and the first detectable sign of approaching menopause.[1]

There are three phases of endocrinal changes at climacteric as follows:

Phase I: Hypothalamic Pituitary Hyperactivity

- Starts 5 to 15 years before menopause
- Compensatory for increased resistance of ovarian follicles and reduced follicular hormone secretion
- Evidenced by elevated FSH and later luteinizing hormone (LH) associated with hot flushes. The pituitary become exhausted in late menopause.

Phase II: Ovulation and Corpus Luteum Failure

- Anovulatory cycle and shortened luteal phase
- Deficient progesterone and unopposed estrogen secretion may lead to abnormal uterine bleeding (AUB), endometrial hyperplasia.

Phase III: Ovarian Follicular Failure

- Failure in follicular development lead to reduced estrogen
- Ovarian stroma remain active along with adrenals-produce androstenedione and testosterone. Estrogen produced by peripheral conversion.

DIAGNOSTIC CRITERIA FOR MENOPAUSE

A. Cessation of menstruation for consecutive 12 months during climacteric.
B. Appearance of menopausal symptoms 'hot flush' and 'night sweat'.
C. Vaginal cytology showing maturation index of at least 10/85/5 (low E).
D. Serum estradiol: <20 pg/ml.

E. Serum FSH and LH: >40 m IU/ml (three values at weeks interval required).

Menopausal Symptoms

Apart from cessation of menstruation some of following symptoms may appear in different women:[1-4]

1. Vasomotor symptoms
2. Urogenital symptoms
3. Osteoporosis and fracture
4. Cardiovascular disease
5. Cerebrovascular disease
6. Psychological changes
7. Skin and hair
8. Breast changes
9. Sexual dysfunction
10. Ophthalmic dysfunction (keratoconjunctivitis sicca)
11. Dementia and cognitive decline.

MANAGEMENT

Management should depend on nature as well as severity of the problems of menopause. It should be such that a women can say that 'for me no pause.' Most of the time general management is enough after excluding organic disease. Hormone replace therapy (HRT) is now being tried to be replaced by nonhormonal preparations for the following reasons:[2,4]

I. Medically unfit for HRT
   1. Cardiovascular disease
   2. Breast cancer
   3. Undiagnosed vaginal bleeding
   4. Newly diagnosed or uncontrolled high blood pressure
   5. Severe or active liver disease with abnormal liver function test results.

II. HRT has been tried but not tolerated.

III. A more natural approach is desired.

General Management

1. Assurance that it is a natural change of life, not an end of life and should be taken as an opportunity to take up new interest and activities.[3]
2. Good diet-including milk, beans, broccoli, spinach, cereals, legumes and fish.
3. Appropriate exercise–running, aerobics, weight lifting, climbing stairs and brisk walking. Regular exercise not only helps with weight loss but also reduces flushes, the risk of heart disease and the risk of osteoporosis. Increasing exercise has also been shown to reduce the risk of breast cancer.
4. Avoid smoking, alcohol, coffee, excessive salt and erated drinks.
5. Multivitamines:
   Vitamin A—for healthy immune system.
   Vitamin B—B6 may have a role in the prevention of heart disease by lowering harmful homocysteine levels, which are associated with heart disease, stroke, osteoporosis and Alzheimer's disease.
   Vitamin C—it works as an antioxidant.
   Vitamin D—it helps the body absorb calcium.
   Vitamin E—protective effect against heart disease. It has been found to reduce the number of nonfatal heart attacks, but not fatal ones. A dose of 400 to 800 IU is suggested. High dose Vitamin E also helps with night flushes. It is also known for its beneficial effects on skin and hair.
6. Minerals:
   Calcium: During the menopause, an adequate daily calcium intake is especially important to help protect and maintain bone density as bone loss accelerates. Phosphorus is a necessary nutrient. Magnesium supplements of at least 250 mg per day may help prevent bone loss. Iron deficiency is still common in women specially in India. Zinc helps with skin repair and damage and also promotes a healthy immune system. Copper supplements should be taken along with the zinc.

   Copper: Small doses of copper can possibly prevent bone loss.

   Manganese: A highly processed diet of convenience food could result in low levels of manganese intake. Iron and manganese are best taken together.

   Selenium: Supplements of selenium have been associated with a reduction in cancers.
7. Relaxation, massage, acupressure, reiki, aroma, yoga and meditation also helps in joint pains as well as psychomotor symptoms.[3]

Specific Management

Hot Flushes

1. Clonidine—alpha adrenoceptor agonist help in hot flushes. This is used for migraine or high blood pressure. The dose ranges from 2 to 3 (25 mcg) tabs two times per day according to response. It is usually well tolerated but possible side effects include difficulty in sleeping, dry mouth, dizziness, constipation and sedation.[5,6]
2. Slective serotonin reuptake inhibitors (SSRI) and serotonin and noradrenaline reuptake inhibitors (SNRI)-fluoxetine, paroxetine, citalopram and venlafaxine

(37.5 mg bid) shows 65% reduction in hot flushes at 12 weeks.[3] These antidepressant drugs work on the 'thermostat' receptor as well as neurotransmitters. Examples are venlafaxine (Effexor), fluoxetine (Prozac) and paroxetine (Paxil). They have been studied and widely used effectively for reducing flushes in women who have had breast cancer. Care should be taken however, if tamoxifen is being taken as part of the treatment for breast cancer as some SSRIs may interfere with the action of tamoxifen. Venlafaxine seems to be less likely to have this effect and so is the preferred option in this situation.[7,8] The dose of SSRIs can be started low and increased gradually to minimize side effects like nausea, dizziness, sleep disturbance, agitation and confusion.[10-14]

3. *Gabapentin (Neurontin)*—gama-butyric acid analog—It is primarily used to treat epilepsy, migraine and nerve-related pain. It also reduce flushes by 50% and in a single bedtime dose of 900 mg by 50%.[15] It may be particularly beneficial for the symptoms of aches, pains and paresthesia which many menopausal women suffer. Possible side effects include dizziness, fatigue, tremor and weight gain but side effects can be reduced by starting at a low dose and increasing the dose gradually.
4. CNS—active medicinal plants like Ashwagandha (Withania somnifera Dunn), Bhallatak (Semicarpus Anacardium Linn), Yashtimadhu (Glycyrrhiza glabra linn), Bala (Sida cordifolia) are important Ayurvedic medicinal plant with rasayan (rejuvenating) and phytoestogenic properties.[16-18] Black Cohosh is found effective not more than pleccebo.[9,14]

OSTEOPOROSIS

1. Bisphosphonates—prevent osteoclastic bone resorption reduces vertebral and nonvertebral fracture by 50%. First generation bisphosphonate, etidronate, also inhibits bone mineralization and hence intermittent therapy like 400 mg daily for 2 weeks followed by 12 weeks, only calcium.[3,19,20]

   Alendronate (5 mg/day or 35 mg/week) reduced the risk of vertebral fracture by 90% and nonvertebral fracture by 30 to 50% in the first 3 years of treatment.[14,21-23] It should be taken empty stomach with full glass of water and should remain upright for 30 minutes to prevent esophagitis. Risedronate and ibandronate are also effective and have less side effect.
2. Calcitonin—natural polypeptide derived from Salmon and eels, regulate plasma calcium, can be given 100 IU/day subcutaneous or 200 IU/day as nasal spray has same effect as estrogen conserving bone density.[14] It should be combined with calcium and vitamin D.
3. Fluoride—25 mg a day combined with calcium reduces vertebral fractures as it increases trabecular bone mass but adversely affect cortical bone and can increase risk of hip fractures.[29]
4. Strontium ranelate—alkaline earth element like calcium reduces the vertebral and hip fracture (2 gm sachet/day).
5. Raloxifene (SERM)- 60 mg/day. Found with reduction in vertebral and nonvertebral fracture as well as breast cancer like tamoxifen. There is 44% reduction in vertebral fracture.[24,25]
6. Tibolone—largest trial (WHI women health initiative) reported adverse effect of estrogen and progesterone therapy, synthetic steroid provide estrogenic effect over bone which inhibit bone resorption 2.5 mg/day S/D are weight gain, fluid retention, bleeding p/v in first 3 months and disappear after.[26]
7. Calcium supplementation—improved calcium intake in adolescence increase bone density and skeletal mass that provide more protection against osteoporosis.[27] More calcium is needed 500 to 1,000 mg/day in women not on HRT.[29]
8. Vitamin D—20 mg/day decrease incidence of hip fracture by 43% and nonvertebral fracture by 32%.[13,14]
9. Teriparatide—recombinant parathyroid hormone has action on osteoblast with dose of 20 to 40 mcg/day subcutaneously.[28,29]
10. Thiazide—given as antihypertensive, reduce urinary loss of calcium and induce positive calcium balance.

CARDIOVASCULAR DISEASE

SERM: MORE (multiple outcomes of raloxifene evaluation) trial result showed decrease in cardiovascular accidents by 40 to 60%.[9-11]

1. Vitamin E—400 IU/day, by inhibiting the oxidation of LDL-cholesterol and inhibiting platelet aggregation. It also decreases fatigue, nervousness, dizziness, headache, palpitations, joint pain and backache.
2. Vitamin B6, B12 and folic acid—facilitate conversion of methionine to harmless amino acid cystathionine and protect against cardiovascular disease.

PSYCHOMOTAR SYMPTOMES

Anxiety can be relieved by yoga and uses of anxiolytics.[30,31]

DYSPAREUNIA

1. Regular coitus avoids dyspareunia and other minor sexual problems.[4,32]
2. Vaginal lubricant and moisturizer (Lubic ointment) can be used for the same.[32]

SUMMARY

Tibolone

Benefits

1. Vasomotor symptoms—significantly beneficial equivalent to estrogen.
2. Psychological symptoms—positive effect on mood and insomnia.
3. Urogenital tract and libido-improve.
4. Cardiovascular system—reduce triglycerides, cholesterols, lipoproteins and high density lipoproteins (HDL) while unaltered low density lipoproteins (LDL).
5. Osteoporosis—prevent bone loss.

Risks

Weight gain and breakthrough bleeding.

Raloxifene

Benefits

1. Cardiovascular disease –beneficial.
2. Osteoporosis—significant reduction in bone turnover. No effect on vasomotor, urogenital and psychological symptoms.

Risks

May worsen hot flushes, leg cramps and vaginal bleeding. Phytoestrogens: There are four classes of phytoestrogens that have been most investigated: isoflavones, lignans, flavones and coumestans. Isoflavones are the most common form and include genistein, daidzein and glycitin have shown in some clinical trials to reduce hot flushes significantly, although many of the trials were undertaken over short periods, e.g. 3 months and some trials have shown limited effect. To rely on dietary intake alone would involve the ingestion of large amounts of legume food plants, such as peas and beans, with variation in their quantities of phytoestrogens. There are many supplements now available which aim to be equivalent to a typical Japanese diet rich in phytoestrogens.

Novogen Red Clover is an excellent source of several isoflavones. There are many other options on the market but this one is well studied and tested and is made from a standardized extract. Red clover or promensil in the USA has been endorsed by the food and drug administration as cholesterol lowering and prostate cancer reducing.

Phytoestrogens or plant estrogens in our diets.

Cereals: Oats, barley rye, brown rice, couscous and bulgar wheat.

Seeds: Sunflower, sesame, pumpkin, poppy, linseeds.

Pulses: Soya beans and all soya-based products (except soya sauce which does not contain any!).

Beans: Chickpeas, kidney beans, haricot beans, broad beans, green split peas.

Vegetables: Red onions, green beans, celery, sweet peppers, sage, garlic, broccoli, tomatoes and bean sprouts.

Soya, linseeds and red clover are the richest sources.

Commercial products are also available such as burgen bread, provamel yogurts and 'so good' milk.

Some women need to be cautious of taking these supplements—e.g. if they are currently suffering from breast cancer or other hormone-dependent tumors. Some breast surgeons and oncologists believe that even the tiny amounts of estrogen can have an adverse effect, but opinion is currently divided.

CONCLUSION

Diet rich in proteins, calcium, vitamin D and other micronutrients since childhood results in better bone mass density at puberty and lesser fractures during menopause. Aerated drinks, alcohol, smoking and steroid for long-time should avoid. Physical activities and exercises play important role in prevention of osteoporosis and mood swings.

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