

Hormone Replacement Therapy and Menopause

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Menopause

- Menopause is a physiological event. It is the permanent cessation of menstruation which occur when the ovarian follicular pool is depleted. On average, it occurs at the age of 51. The transition time before menopause takes 2 to 8 years before menopause. During menopause, there are increased levels of LH and FSH due to the loss of negative feedback.
- Women spend 1/3 of their lives postmenopausal considering the mean age of menopause 51 and life expectancy around 80 years old.



Definition of Hormone Replacement Therapy

- Hormone replacement therapy (HRT) is this type of therapy which contain one or more female hormones, commonly estrogen plus progestin (synthetic progesterone). Women who have had their uteri removed, receive estrogen-only therapy (ERT). Testosterone may be added in cases with diminished libido.
- HRT is used to treat menopausal symptoms such as hot flashes, vaginal dryness, mood swings, anxiety, depression, sleep disorders, and decreased libido. HRT is available in different forms such as a pill, patch, vaginal cream or rings.



Forms of Hormone Replacement Therapy

1-The pill:

a-Cyclic hormone therapy: Estrogen is taken in pill form for 25 days, with progestin added from day 15. Both are then continued till day 25. Then, no pills are taken for 5 days to allow for monthly withdrawal bleeding.

b-Continuous combined therapy: Both estrogen and progestin are taken together daily. When this therapy is started, or when switching from cyclic to continuous therapy, women may experience irregular bleeding which usually stops in 1 year after starting therapy.



Forms of Hormone Replacement Therapy (Cont)

2-The skin patch:

It can be applied to the abdomen or the thigh. The patch allows the estrogen to be absorbed through the skin into the bloodstream.

3-Vaginal estrogen cream:

This is mainly given to women for vaginal dryness. The cream is usually given together with a systemic HRT because the cream may not relieve many of the other menopausal complaints.



History of HRT

- In 1920, Hormonal therapy was first used.
- In mid 40s. FDA approved the use of premarine (Conjugated equine estrogen) to control menopausal symptoms.
- In mid 70s, unopposed estrogen use was found to increase endometrial cancer.
- Progesterone was found to abolish the estrogen dependant endometrial cancer risk



Review of The Observational Trials

-In 1976, HRT was found to decrease the risk of osteoporosis in women after menopause.

-In 1981, It was shown that HRT provides cardio-protective effect to postmenopausal women.

-In 1988, HRT was claimed to reduce mortality and risk of Alzheimer's disease in postmenopausal women.

The accelerated use of HRT paralleled the results shown by these studies.



Review of The Randomized Controlled Trials

1-In 1998, the Heart Estrogen/Progestin Replacement study (HERS) showed that HRT does not provide any cardio-protective effect for women in their postmenopausal years.

2-The results of the Women's Health Initiative trial (WHI) were released mid 2002. HRT was thought to prevent cardiovascular events and prevents bone loss in postmenopausal women. The WHI study showed that among postmenopausal women under HRT, there is:



Review of The Randomized Controlled Trials

(Cont.)

Side Effects

a-41% increased risk of strokes: There is increased risk with both HRT & ERT

b-29% increase in heart attacks: The number of heart attacks increased among women taking E+P HRT.

c-Doubled incidence of venous thrombo-embolism

d-22% increase in cardiovascular diseases

e-26% increase in cancer breast

On the other hand, there was 22% decrease in total bone fractures of them 1/3 decrease in hip fractures. There was 37% reduction in the incidence of colorectal cancer.

Review of The Randomized Controlled Trials (Cont.)

- A subgroup analysis of the WHI showed that women who started HRT closer to menopause had a reduced risk for coronary heart disease rather than increased risk as seen in older women more distant from menopause.
- 3 In agreement with this analysis, the WISDOM trial published in 2007 found that in women distant from the start of menopause, HRT resulted in significantly more major cardiovascular & thrombo-embolic events compared to placebo. There was no significant differences in numbers of breast or other cancers, cerebro-vascular events or overall deaths. On the other hand, there was a marked, not significant, reduction in osteoporotic fractures at one year, a finding similar to that seen in WHI study.



Limitations of the WHI

1-Only prempo – which is a form of continuous HRT consisting of conjugated equine estrogens and medroxyprogesterone acetate, and premarin in women with surgical menopause were used. Women on Premarin alone did not have the same increase in breast cancer risk as those on the Prempro and therefore, it was suggested that the progestin component may be responsible for increased risks of cancer when taken in conjunction with the Premarin.

2-Only the oral route was used.



Indications

Short term use of hormone replacement therapy is indicated to control hot flushes, mood swings & vaginal dryness.

Long term or chronic use of hormone replacement therapy to prevent osteoporosis is no longer recommended.



Contraindications for HRT

Absolute:

- 1-Coronary heart disease and severe liver disease
- 2-History of DVT or pulmonary embolism.
- 3-Undiagnosed vaginal Bleeding
- 4-Estrogen dependant tumors.

Relative:

- 1-Migraine headaches
- 2-Personal history of breast cancer and/or fibroid
- 3-Atypical duct hyperplasia of the breast
- 4-Active gall bladder disease (Cholangitis, Cholecystitis)

Alternatives to Hormone Replacement Therapy

Indications:

- 1-Prevention of Osteoporosis
- 2-Prevention of cardiovascular events



Types of Alternatives to Hormone Replacement Therapy

I-Life Style Changes:

1-Diet

- Eat balanced diet of natural food. e.g. fresh fruits, vegetables, whole grains, seeds & nuts. Avoid canned & spicy foods.
- Calcium supplementation. The recommended daily intake ranges between 1200-1500 mg. Foods rich in calcium include milk, dairy products & leafy green vegetables . Calcium supplements should be taken with food.
- Vitamin D supplements. The daily intake should be 400-600 IU in the presence of 15 mins sun exposure & 800 to 1000 IU in the absence of sun. Examples of foods rich in vitamin D are fortified milk, liver, and tuna.

Types of Alternatives to Hormone Replacement Therapy (Cont.)

- Consume more phyto-estrogenic foods such as soya, corn, apples, bananas, cashew nuts, oats, broccoli, cauliflower & green leafy vegetables.
- Avoid excessive sweets which can cause a surge in blood sugar. Hot flushes may be related to fluctuations in blood sugar levels.
- Drink enough water/day. Avoid coffee in the evening. Minimize fizzy drinks.



Types of Alternatives to Hormone Replacement Therapy (Cont.)

2-Regular exercises: maintain bone density, prevent weight gain & enhances the immune system. Exercise may be in the form of daily walking, Swimming or yoga.

3-Obtain adequate sleep and avoid eating before going to bed.

4-Reduce Stress: listen to your favourite music, go for a walk ..etc.



Types of Alternatives to Hormone Replacement Therapy (Cont.)

II-Alternative Medicine:

A-Herbs: There are basically two types of herbs for natural alternatives for hormone replacement therapy: phytoestrogen and non-estrogenic herbs.

1-The phytoestrogen herbs: (e.g. Black Cohosh, Dong Quai) contain estrogenic components produced by plants. They replace some of the missing estrogen hormones.



Types of Alternatives to Hormone Replacement Therapy (Cont.)

2-Non-estrogenic herbs: These do not contain any estrogen. They stimulate the pituitary and endocrine glands to work more efficiently and produce more natural hormones. This ultimately ends up in balancing your own body's hormonal milieu. E.g. Macafem

B-Acupuncture: useful in the treatment of hot flashes as well as manifestations of anxiety and depression.



Types of Alternatives to Hormone Replacement Therapy (Cont.)


III- Selective Estrogen Receptor Modulators (SERMs)

These are a class of medication that acts on the estrogen receptor. A characteristic that distinguishes these substances from pure receptor agonists and antagonists is that their action is different in various tissues, thereby selectively inhibit or stimulate estrogen-like action in various tissues. They include clomiphene, Raloxifene, Tamoxifen, Toremifene, Bazedoxifene, Lasofoxifene, and Ormeloxifene



Types of Alternatives to Hormone Replacement Therapy (Cont.)

Actions of SERMs:

- 1-Pituitary: Clomiphene blocks estrogen action, leading to an increase of FSH.
 - 2-Uterus: Tamoxifen increase endometrial carcinoma risk.
 - 3-Breast: All SERMs decrease breast cancer risk. Tamoxifen is used for its ability to inhibit growth in estrogen receptor-positive breast cancer.
 - 4-Cholesterol and triglycerides: respond favorably to SERMs.
 - 5-Postmenopausal osteoporosis respond favorably to SERMs.
 - 6-DVT: The risk may be elevated in all SERMs.
 - 7-Hot flashes are increased by all SERMs.
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Types of Alternatives to Hormone Replacement Therapy (Cont.)

1-Raloxifene (EVISTA):

- An estrogen agonist/antagonist indicated for:
 - Treatment and prevention of osteoporosis in postmenopausal women
 - Reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis
 - Reduction in risk of invasive breast cancer in postmenopausal women at high risk for invasive breast cancer
- Limitations: EVISTA is not indicated for the treatment of invasive breast cancer, reduction of the risk of recurrence of breast cancer, or reduction of risk of noninvasive breast cancer.



Types of Alternatives to Hormone Replacement Therapy (Cont.)

2-Tamoxifen (Nolvadex):

Advantages:

- a-It decrease risk of breast cancer by 49%.
- b- It decreases risk of hip fractures by 45% and increases bone mineral density slightly (1-1.4%),

Disadvantages:

- a- May increase uterine cancer risk.
- b-Increases heart disease risk by 15%
- c- Increases risk of thrombo-embolism 2-3 times, but does cause a



Types of Alternatives to Hormone Replacement Therapy (Cont.)

IV-Other alternatives:

- 1-Antidepressants: Selective serotonin reuptake inhibitors was found to decrease hot flashes. Examples include Venlafaxine (Effexor), fluoxetine (Prozac), paroxetine (Paxil), citalopram (Celexa) and sertraline (Zoloft).
- 2-Gabapentin (Neurontin). Significantly reduce hot flashes.
- 3-Clonidine (Catapres): An antihypertensive which was found to reduce the frequency of hot flashes but has numerous side effects.
- 4-Bisphosphonates: A class of drugs used to prevent or treat osteoporosis. e.g. alendronate (Fosamax), risedronate (Actonel) & ibandronate (Boniva).



Types of Alternatives to Hormone Replacement Therapy-New Horizons (Cont.)

V-Tissue Selective Estrogen Complex (TSEC):

Researchers from Wyeth Pharmaceuticals reported on a new class of drugs which combined a conjugated equine estrogen (Premarin) with toremifene, a drug commonly known as a SERM.

They claimed that the new drug relieve hot flashes, improves vaginal dryness and also maintains bone mass while decreasing the risks associated with traditional HRT.



Thank You

