

# Postmenopausal hormone therapy

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## Oestrogen production before menopause in women

The primary oestrogen from puberty to menopause is oestradiol produced by the ovaries, which circulates in the blood and acts throughout the body.

Throughout life the ovaries and adrenal gland also produce hormones called androstenedione, testosterone (T), dehydroepiandrosterone (DHEA) and DHEA-sulphate (DHEAS) each of which may be converted to oestradiol and oestrone by the enzyme aromatase in many parts of the body.

Following menopause, when the ovaries cease to produce oestrogens, oestrogens are primarily produced in other parts of the body, mainly in fat tissue, bone, brain and blood vessels.

Thus women who have more body fat produce more oestrogen after menopause and are more at risk of uterine cancer, and thinner postmenopausal women lower circulating oestrogen is associated with a greater risk of fracture.

In postmenopausal women the most of the oestrogen in the circulation is oestrone sulphate, levels of which have been measured at ten to twenty-five times greater than levels of oestradiol. Oestrone sulphate circulates for quite a long time in the blood (has a long plasma half-life and slow clearance rate) and thus acts as a reservoir for the formation of oestradiol in other tissues.

Oestradiol circulates in the blood partly bound to a protein called sex hormone binding globulin (SHBG). Therefore when a woman has high levels of this protein called SHBG less oestrogen is available to act in the cells. Thus different blood levels of SHBG impact significantly on the amount of free, or bioavailable oestradiol and this has significant therapeutic implications.

## Oestrogens as hormone therapy

The primary use of postmenopausal hormone therapy (HT) is to alleviate symptoms of the menopause, namely hot flushes, night sweats, sleep disturbance and vaginal dryness and therefore improve the quality of life of women who without HT find these symptoms intolerable.

- For women with an intact uterus progestin therapy is taken with oestrogen to protect the lining of the uterus from over stimulation by oestrogen. This can be cyclic ie for 14 days out of a monthly cycle, or as continuous-combined HT when both the oestrogen and progestin are taken every day. Cyclic HT results in scheduled menstrual bleeding; whereas no bleeding occurs with continuous-combined HT.
- For women who have undergone a hysterectomy the administration of oestrogen therapy (ET) alone is appropriate.

Oestrogens are naturally occurring hormones or synthetic steroidal or nonsteroidal compounds with oestrogenic activity. Various oestrogens are in use for therapy.

Taken as an oral tablet, oestradiol is absorbed and metabolized by the gut lining and the liver, so that only 10 per cent reaches the circulation as oestradiol. This metabolism in the gut and liver converts a large proportion of oestradiol to oestrone. Thus, measurement of serum oestradiol is not useful for monitoring oral estrogen replacement.

The most widely used oestrogen preparation worldwide in postmenopausal women continues to be oral conjugated equine oestrogen (CEE). Oral CEE has been available for more than 50 years. CEE are prepared from the urine of pregnant mares and are composed of 50–60 per cent oestrone sulphate with multiple other equine oestrogens such as equilin and 17 – dihydroequilin.

Other oral oestrogen preparations include synthetically derived piperazine oestrone sulphate, oestriol, micronised oestradiol and oestradiol valerate. Oestradiol may also be given transdermally as a patch or gel, as a slow release percutaneous implant, and more recently as an intranasal spray. Intravaginal oestrogens include topical oestradiol in the form of a ring or pessary, oestriol in pessary or cream form.



Oral oestrogen preparations may result in up to 10 fold higher levels of circulating oestrone sulphate than oestradiol administered as a skin patch/gel at comparable or even higher doses. Oestrogen sensitive tissues such as breast and the uterus have a high capacity to convert oestrone sulphate to oestradiol. This may be a prime mechanism by which concentrations of oestrone and oestradiol in breast cancer tissue are several fold greater than circulating levels. **Orally oestrogen therapy also increases SHBG** to a greater extent than non-orally administered oestrogens and this will reduce the amount of hormone available to the tissues, including a woman's own testosterone which is also bound to SHBG.

Thus it would seem that the prescription of oral oestrogen therapy should be at the lowest available dose to minimise effects on circulating oestrone sulphate and SHBG. Consistent with this, lower dose combinations of oral oestrogen plus progestin are associated with equivalent symptom relief as higher dose combinations but lower rates of breast tenderness and vaginal bleeding.

**NON oral oestrogen administration** results in a more natural balance between oestradiol and oestrone. It can be very useful for women with elevated triglyceride levels or significant liver function abnormalities. Non oral therapy is also less likely to affect SHBG.

**Transdermal patches or gels** deliver oestradiol to the general venous circulation at a continuous rate. Local skin reactions to the patches occur in about five per cent of women. **The incidence of skin irritation diminishes when women rotate the application site.**

**Skin gel** preparations are convenient and have been available for over 20 years.

**Oestradiol pellets** (implants) containing pure crystalline oestradiol have been available for over 50 years. They are inserted into the superficial fat of the lower abdominal wall through a very small (1cm) incision. Pellets are difficult to remove and may continue to release oestradiol for a long time after insertion. Thus, implantation should not be repeated until the serum oestradiol levels have fallen to a value similar to that seen in a premenopausal women during the early to mid phase of the menstrual cycle.

**Vaginal rings** are a sustained delivery system composed of a biologically inert liquid polymer matrix with pure crystalline oestradiol that maintain adequate oestradiol levels.

**Vaginal estrogens** have been used for treatment of vaginal dryness and atrophy. At low doses, local application can reverse menopausal vaginal changes and there is little to no significant absorption into the circulation.

Oestrogen therapy is occasionally prescribed as "**bio-identical**" **therapy** and individual prescriptions are made up by a compounding pharmacist. Women are often told that their prescription has been individualized to 'balance their hormones' however there is no proven formula for estimating how much oestrogen any individual woman will need to relieve her symptoms based on her postmenopausal blood levels. There is also no single blood level known to be right for an individual as women vary greatly. In addition women are often advised that compounded prescriptions are more bio-identical as they contain the three oestrogens their bodies need. However, when a woman taken oestradiol alone, her body will very cleverly create the balance she needs of the different oestrogens in the way that is natural for her. The main concern regarding compounded oestrogen is that no studies have been undertaken as to what dose is safe and how much progestin is needed to protect the uterus from cancer.

Usually, the initial dose of ET is the minimally effective dose necessary to relieve vasomotor symptoms. A low dose of oral conjugated equine oestrogen (0.3 mg/day) is equivalent to a daily transdermal dose of 25g of oestradiol or 1mg of oral micronized oestradiol. If side effects occur, such as breast tenderness, lowering the dose may resolve the problem. On the other hand, if symptoms are not being adequately controlled, there is an option to increase the estrogen dose.

#### Side effects

Common side effects of too much oestrogen include nausea, headaches, breast tenderness, and heavy bleeding. Commencing all women initially on low dose therapy will minimize breast tenderness, unscheduled bleeding and other potential side effects. Transdermal oestrogen is less likely than oral oestrogen to cause headache and nausea. Also, transdermal oestrogen causes less breast tenderness and deep vein thrombosis than oral oestrogen.

Changing from one oestrogen regimen to another may be enough to decrease side effects.

#### Progestins as hormone therapy

Because of the increased risk of endometrial thickening (hyperplasia, a precancerous change in the uterine lining) and endometrial cancer with oestrogen use alone (**unopposed oestrogen**), women who have not undergone hysterectomy should also take a progestin with their estrogen. Progestins reduce oestrogen receptor concentrations, suppress DNA synthesis and decrease oestrogen activity in the uterine tissues.

**Standard doses of progestins have been established to prevent endometrial thickening for approved oestrogen therapies. This is not the case for compounded hormone preparations.**

It is important that the progestin is taken for long enough in each cycle to be effective. A minimum of 12–14 days of progestin each month is required for complete protection against estrogen-induced endometrial hyperplasia. There is rarely a need for progestin administration in women who have undergone hysterectomy.

Progestins can be used in combination with oestrogen in a cyclical fashion for 12–14 days of the month or daily throughout the month (continuous combined HT).

**Cyclical HT** results in scheduled vaginal withdrawal bleeding, although in older women this may be scant or not all. Continuous combined HT ultimately results in endometrial atrophy and the absence of vaginal bleeding. Various combinations of estrogen plus progestins are commercially available.

The first generation of progestins contained the C-19 androgenic progestins norethisterone, norgestrel, and levonorgestrel. More recent preparations have included the C-21 progestins dydrogesterone and medroxyprogesterone acetate (MPA), which are less androgenic. Micronized progesterone (MP) is not as yet available for use in postmenopausal women in Australia. A vaginal levonorgestrel impregnated intra uterine device (IUD) is available in Australia and in appropriate circumstances is an excellent option for progestin effects to be achieved in the endometrium with minimisation of some side effects. Commonly used oral progestins are MPA, dydrogesterone and norethisterone acetate. The latter can also be administered transdermally in the combined estrogen-progestin patch.

**Non prescription and prescribed progesterone creams** are widely available and are being used by many women with the belief that this treatment will preserve bone, act as an alternative to hormone therapy, may be substituted for synthetic progestins in HT regimes and alleviate menstrual and pre menstrual symptoms. It has been claimed that progestin cream results in improvement in bone density in postmenopausal women over three years. However an unknown number of participants in the study supposedly supporting this claim were also treated with oral oestrogen. With respect to effectiveness in protecting the endometrium, studies of progesterone cream have produced mixed results. Some studies indicate that if a sufficient amount of progesterone can be administered, transdermal progesterone may alleviate vasomotor symptoms and afford endometrial protection short term, but long term benefit and safety need to be established. There is no evidence that transdermal progesterone cream prevents bone loss.

#### Side effects

Common side effects of progestin include irritability, depression, and headaches. Natural micronised progesterone taken orally may induce sedation and undesirable hypnotic effects. Changing from cyclic to continuous regimen, or changing from one progestin to another may decrease these side effects.

Side effects of progestins are difficult to evaluate and vary with the progestational agent administered. Some women experience "premenstrual like" symptoms, such as mood swings, bloating, retention of fluids and sleep disturbance. Switching among various progestational agents may decrease these symptoms.

Women who are unable to tolerate a progestin may be given unopposed estrogen if they are informed of the significant increased risk for endometrial cancer and have endometrial biopsy annually or whenever vaginal bleeding occurs.

#### IS HT dangerous?

The American Endocrine Society has published a position statement of the use of postmenopausal hormone therapy in 2010. This is the result of a rigorous review of the published studies of post-menopausal hormone therapy. The conclusions reached from a position statement based on level A evidence as follows:

- "Standard-dose" **estrogen used with or without a progestin** is associated with marked reduction in frequency and severity of hot flushes. For many women, lower doses of estrogen are also effective.
- For symptoms of vaginal atrophy, very low doses of vaginal oestradiol are effective.
- Symptoms of overactive bladder may be reduced by oestrogen given vaginally or systemically.
- Vaginal oestrogen is associated with lower rates of recurrent urinary tract infections.
- For women in late postmenopause, oestrogen given with or without a progestin is as effective as bisphosphonate therapy for preventing early postmenopausal bone loss and increasing bone mass.

- Use of oestrogen alone and oestrogen plus a progestin is associated with a lower incidence of hip and vertebral fractures.
- Use of HT containing oestrogen plus a progestin is linked to a lower risk for colon cancer.
- Mammographic density is increased in women taking oestrogen alone or with a progestin.
- Risk for venothrombotic episodes is approximately doubled in women using HT, and this risk is multiplicative with baseline risk factors such as age, increased body mass index, thrombophilias, surgery, and immobilization.
- In older women with preexisting vascular disease, hormone use does not reduce stroke incidence.
- Although continuous estrogen plus a progestin does not cause endometrial cancer, oestrogen alone without a progestin is associated with an increased incidence in endometrial cancer.
- Risk for gallbladder disease is increased in women using estrogen alone or with a progestin.
- HT started after age 60 years does not improve memory.
- An alternative hormonal therapy for postmenopausal vasomotor symptoms is tibolone, which is widely available worldwide, but not in the United States.
- Tibolone improves urogenital atrophy.
- For osteoporotic women older than 60 years, tibolone is associated with significantly lower rates of vertebral and nonvertebral fractures.
- In older, but not younger, women, tibolone is associated with an increased risk for stroke.
- Tibolone is not associated with an increased incidence of endometrial hyperplasia or carcinoma.
- Use of tibolone is associated with a greater risk for breast cancer recurrence in women with breast cancer.
- Treatment with the selective oestrogen receptor modulator raloxifene is associated with increased bone mineral density and lower rates of vertebral, but not hip, fractures.
- Raloxifene is associated with a lower risk for breast cancer.
- Sexual function is improved by physiologic amounts of transdermal testosterone, but not by dehydroepiandrosterone.
- Use of raloxifene is associated with an increased incidence of venothrombotic episodes.
- Raloxifene is not associated with any increase in stroke risk.