



OESTROGEN AND PROGESTIN AS HORMONE THERAPY

Oestrogen production 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 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 oestradiol 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 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 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.

After oral administration, oestradiol is absorbed and metabolized by the intestinal mucosa and the liver during the first hepatic passage, so that only 10% 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 is 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% oestrone sulphate with multiple other equine oestrogens such as equilin and 17α -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 transdermally administered oestradiol at comparable or even higher doses. Oestrogen sensitive tissues such as breast and endometrium have 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 physiological 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 5% of women who use matrix (estrogen in



adhesive) patches, respectively. **The incidence of skin irritation diminishes when women rotate the application site.**

Percutaneous gel preparations are convenient and have been available in France for over 20 years.

Oestradiol pellets (implants) containing pure crystalline 17β -oestradiol have been available for over 50 years. They are inserted subcutaneously into the anterior abdominal wall or buttock. 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.

An **intranasal 17β -estradiol spray**, which enables pulsatile therapy in a single daily or twice daily dose, has been developed for use in postmenopausal women and is now available in many countries.

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 3 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 25 µg of oestradiol or 1 mg 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 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 oestradiol receptor concentrations, suppress DNA synthesis and decrease oestrogen activity in the uterine tissues.

Standard doses of progestins have been established to prevent endometrial hyperplasia 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 HRT). Cyclical HT results in scheduled vaginal withdrawal bleeding, although in older women this is 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 levonogestrel. 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 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

MONASH University

Produced by the Women's Health Program, Monash University©

<http://womenshealth.med.monash.edu.au>



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.

MONASH University

Produced by the Women's Health Program, Monash University©

<http://womenshealth.med.monash.edu.au>

