Current trends in hormone replacement therapy

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ABSTRACT

As life span increases, more and more women live longer after the menopause, and see its long-term consequences. The menopause and climacteric have major consequences for the well being of most women, resulting in a variety of symptoms including vasomotor, psychological, sexual symptoms and increased risk of osteoporosis and atherosclerosis. Prevention of osteoporosis and reduction in cardiovascular risks are the long-term goals of post-menopausal hormone replacement therapy. Post-menopausal women who receive hormone replacement therapy have approximately half of the rate of coronary artery disease compared to those who do not take it. Similarly, estrogen replacement alone for 5 years results in 50% reduction in the risk of overall fracture and is a major factor in the prevention and management of osteoporosis. A wide range of estrogen preparations is available for administration by various routes. The choice depends on indications, side effects and convenience. Oral estrogen is the most commonly used preparation followed by transdermal preparation. Controversy still exists over the efficacy and safety of hormone replacement therapy among both the medical and lay authorities. There is overwhelming evidence that hormone replacement therapy improves the quality of life and reduces the morbidity and mortality by reversing the metabolic and pathological changes induced by the menopause. The benefits of hormone replacement therapy out weigh any increased risk of venous thromboembolism or breast, ovarian and endometrial cancers.

Keywords: Menopause, hormone replacement therapy, transdermal, gel, implants.

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The benefits of hormone replacement therapy (HRT) in the relief of menopausal symptoms, urogenital atrophy and protection against osteoporosis[1] and ischemic heart disease,[2] are well established. In addition, there is evidence of possible protection against neurodegenerative disease[3] and beneficial effects on the gut,[4] eye[5] and immune system.[6] Despite this, the acceptance and continuation of HRT therapy remain disappointingly poor. The most frequent quoted reasons are the fear of breast cancer, the unacceptability of the return of monthly withdrawal bleeds, and a premenstrual-like syndrome that can occur during the progestogenic phase of cyclical therapy.[7] This review discusses the range of HRT preparations currently available and their associated risk for gynecological cancers and venous thromboembolism.

Indications. Hormone replacement therapy is not necessarily desired, feasible or required for all climacteric women and some selection based on benefits and risks is essential. Patients meriting hormone replacement include (i) those with climacteric symptoms; (ii) all asymptomatic high risk women (menopause below age 45 years established osteoporosis or fast bone-loser or combination of osteoporotic risk factors; hypercholesterolemia > 6 mol/l) and (iii) all women requesting hormone replacement who are fully informed and have no contraindications.

Contraindications. Contraindications to estrogens are few, and include: (i) previous thromboembolic disease associated with hormonal contraception, pregnancy or estrogen replacement;

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(ii) estrogen-dependent cancers of breasts and endometrium and (iii) liver disease with impaired liver function.

Choice of hormone replacement therapy. The choice of HRT regimen is not straightforward and depends on an overall balance of indication, risk, and convenience. There is no evidence that one type of estrogen is more effective than the others in relieving climacteric symptoms or in preventing osteoporosis or cardiovascular disease. Estrogens may be administered orally, transdermally, vaginally or by subcutaneous implant.

Oral estrogen preparations. Oral estrogen is practically the most convenient preparation to use for most women. Preparations containing the naturally occurring human estrogens,17ß-estradiol, estrone and estriol, are the most widely prescribed in Europe, though world wide conjugated equine estrogens have been used more than any other preparation,[8] especially in North America. All the natural estrogens are derived from plants, cactus or soya bean. Conjugated equine estrogens are prepared from the urine of pregnant mares and are composed of 50-70% estrone sulphate with equine estrogens such as aquilin sulphate and 17∂-dihydroequilin. Conjugated equine estrogens are also considered natural since they tend to behave in a similar way to purely human estrogens. After oral administration, estradiol undergoes metabolism in the small intestine so that only 10% reaches the circulation as estradiol. Further metabolism in the liver converts a large proportion of estradiol to estrone.[9] Absorption of other single estrogens and combinations of estrogen is also affected by metabolism in the intestine and liver, resulting in a predominance of estrone in the circulation.[10] Some of the commonly available oral preparations are listed in **Tables 1, 2 & 3**. The semi-synthetic estrogens, ethinyl estradiol and mestranol, were developed primarily for oral contraception and are generally considered less suitable for HRT due to their more potent effect on hepatic cellular function.[11] Ethinyl estradiol is a stable compound, which is readily absorbed from the intestine and passes unchanged to the liver.[12] Both ethinyl estradiol and mestranol are still used as HRT, particularly for the prevention of osteoporosis.[13] Although, they are much cheaper, there is concern that their greater metabolic effects on the liver than natural estrogens may result in an increased risk of venous and arterial thrombosis.

Non-oral estrogen preparations. Estrogen is absorbed well through skin and subcutaneous fat, vaginal epithelium, nasal and sublingual mucosa. The main advantage of all these routes of administration is that metabolism in the intestine and liver is avoided. **Tables 2 & 4** list some of the non-oral estrogen preparations. (1) Transdermal preparations - the older estradiol skin patches (Estraderm Transdermal System [TTS]) contains a reservoir of estradiol with an alcohol solvent behind a rate limiting membrane and an adhesive layer. Satisfactory circulating estradiol levels are achieved, but local skin reactions can be a side effect in up to 35% of women.[14,15] Newer transdermal systems consist of a single transparent matrix with an adhesive layer, which contains the estradiol. The dose delivered is proportional to the surface area of the patch in contact with the skin. They cause less skin reaction[16] than the alcohol containing reservoir patch. An important disadvantage of the matrix patch however is that it cannot be taken off and reapplied before and after bathing. Most patches have to be changed twice weekly but systems that maintain satisfactory estradiol levels over 7 days are also available (FemSeven and Progynova Transdermal System [TS]). The most commonly used patches are those delivering around 50µg estradiol per 24 hours. There are differences between transdermal and oral estradiol as regards their biochemical effects, particularly related to metabolic risk factors for cardiovascular disease. Both routes of administration lower serum cholesterol, and especially the low density lipoprotein fraction, but serum triglyceride, which may be an independent risk factor for cardiovascular disease,[17] is elevated with oral estrogen[18,19] whereas transferratransdermal estradiol causes a reduction.[20] In addition, oral therapy causes a deterioration in glucose tolerance but there is little impact on glucose or insulin metabolism with transdermal estrogen.[19] There is also no change in coagulation or fibrinolytic factors[21,22] or renin substrate[23] with transdermal estradiol whereas oral conjugated equine estrogens do cause some changes in all these factors.[24,25] (2) Gel preparations - in tropical climates there is a higher incidence of skin reactions from patch preparations and a gel or other route of administration may be more suitable. Estradiol gel is available in a hydro-alcoholic preparation containing 0.06% weight in weight (w/w) 17ß-estradiol or in a non-pressurized canister. A measured dose of 0.75 mg estradiol is dispensed and the usual recommended starting dose is 2 measures daily applied to the arms or legs. Absorption is rapid and effective blood levels are obtained which provide symptomatic relief comparable to oral estrogen.[26] There is no published data on prevention of osteoporosis or cardiovascular disease. A similar gel containing 1mg 17ß-estradiol per gram of gel is also available. (3) Implants - pellets of crystalloid estradiol have been available for subcutaneous implant for over 50 years.[27-29] The most commonly used dose is 50 mg given at 6 month intervals, which produces a circulating level of approximately 400 pmol/L at one year.[30] Good symptomatic relief and protection against osteoporosis are achieved, which may be better than with oral therapy,[30] but each pellet may continue to release estradiol for 2 years or more which can lead to supraphysiological blood levels if

the implants are given too frequently.[31] There is no data to indicate that this situation is hazardous, but for women with a uterus there is a risk of endometrial hyperplasia from prolonged endometrial stimulation. Therefore, after stopping implant therapy, cyclical progestogen should be continued for at least 2 years.[32] The lower dose of 25 mg may reduce this risk,[33] is particularly suitable for older postmenopausal women, and will provide good protection from osteoporosis.[34,35]

Estrogen and progestogen combinations. Unopposed estrogen use in women with uterus may cause proliferation of endometrial tissue and consequently may increase the risk of endometrial carcinoma.[36] Combined treatment with progestogens, in a sequential or continuous regimen, prevents these endometrial abnormalities.[37] The progestogen selected for combined therapy should be well tolerated and free of systemic and metabolic adverse effects. However, some progestogens have adverse effects on the low-density lipoprotein (LDL) high-density lipoprotein (HDL) ratio,[38] suggesting that combined therapy may diminish the cardiovascular benefits obtained with estrogen alone. These metabolic changes are essentially related to the androgenic potency of the progestogen, as are most of the clinical side effects.[39] The ideal progestogen for postmenopausal use should, therefore, protect the endometrium but not reverse the beneficial lipoprotein changes induced by estrogens. Sequential therapy may be provided by a variety of combinations of individual estrogens given by tablet, patch, gel or implant, and oral progestogen. The first generation of oral sequential preparations contained the C-19 progestogens norethisterone, norgestrel and levonorgestrel. More recent preparations have included the C-21 progestogens dydrogesterone and medroxyprogestogene acetate, which are less androgenic, allowing greater flexibility in prescribing particularly in women experiencing premenstrual symptoms such as bloating, depression and headaches during the progestogen phase of treatment. The proprietary oral preparations include 10 to 14 days of progestogen in a 28 day sequential regimen (**Table 4**).

Non-oral progestogen preparations. It has proved much more difficult to deliver progestogen via a skin patch than estradiol, so for sequential therapy additional progestogen is generally taken orally. However, combination patch preparations are now available. Estracombi was the first combination reservoir patch, but now there are 2 single matrix combination patch treatments providing estradiol for 14 days followed by estradiol with either levonorgestrel (Nuvelle TS) or Norethiterone (Evorelsequi) for 14 days (**Table 5**). Unwanted side effects of systemic progestogens may be unacceptable to many women. These side effects may be reduced by the administration of progestogen directly into the uterine cavity in an intrauterine device. The levonorgestrel containing intrauterine device (Mirena) used presently for contraception, will produce an atrophic endometrium, and in combination with estrogen administered orally or transdermally may provide an alternative method of continuous progestogen therapy.[40,41]

Long cycle hormone replacement therapy. Longer cycle HRT, ranging from 3 to 6 months has been evaluated.[42] Since endometrial hyperplasia can be found after 4 months,[43] 3 months may be the longest length of cycle that is safe.[44,45] Currently there is one long cycle medication available (Tridestra) but others are being developed. This preparation contains estradiol valerate 2mg daily for 70 days followed by medroxyprogesterone acetate 20mg in addition to the estradiol for 14 days, which is comparable to monthly sequential regimens, and a rate of endometrial hyperplasia (without atypia) of 1.9% during the first 12 months of therapy.[46]

Continuous combined therapy. Continuous combined therapy regimens may be made up with any estrogen together with a separate progestogen or by using one of the proprietary preparations (**Tables 1, 2, 3, 4 & 5**). The progestogen-only contraceptive pills provide a convenient low dose progestogen supplement and having the progestogen separate allows adjustment of the dose in response to bleeding or side effects.[47] Micronor-HRT contains one mg norethisterone. Alternatively, the gonadomimetic hormone tibolone (Livial) may be used which has estrogenic, progestogenic and androgenic activity and will produce similar effect.[48] Raloxifene, only introduced recently, is a selective estrogen receptor modulator similar to tamoxifen. It acts like an estrogen in the bone and like an estrogen antagonist on the breast and uterus. Raloxifene (60mg daily dose) increases bone mineral density, decreases serum LDL cholesterol levels, but does not stimulate endometrial growth.[49] Its serious adverse effect is venous thromboembolism. More data is still needed on the possible benefits of Raloxifene in heart disease and breast cancer. All these regimens tend to produce an atrophic endometrium in the short term.[50,51] Information on their effects on the endometrium in the long term is not yet available. It is, however, reassuring that in women who develop complex endometrial hyperplasia after taking standard combined sequential regimens for a mean of 2.5 years[52] the endometrium is corrected to normal after changing to a continuous combined therapy preparation.[53,54] Continuous combined therapy may be superior to sequential therapy with respect to endometrial safety.[52] In addition the concordance with continuous combined therapy is better than with sequential therapy.[55]

Vaginal estrogen. Symptoms related to urogenital aging are not well recognized or treated.[56]

Table 1 - Combined oral hormone replacement therapy preparations.

Type	Brand	Estrogen	Formulation	Progestogen
Monthly	Climagest	Estradiol 1mg, 2mg	Tablets	Norethisterone 1mg
	Cyclo-progynova	Estradiol 1mg, 2mg	Tablets	Levo/norgestrel 0.25mg/0.5mg
	Elleste Duet	Estradiol 2mg	Tablets	Norethisterone 1mg
	Femoston	Estradiol 1mg, 2mg	Tablets	Dydrogesterone 10mg, 20mg
	Imropovera	Estrone 0.93mg	Tablets	Medroxyprogesterone 10mg
	Menophase	Mestranol 12.5µg	Tablets	Norethisterone 0.75mg - 1.5 mg
	Nuvelle	Estradiol 2mg	Tablets	Levonorgetrel 0.75mg
	Premique cycle	Conj. Estrogen 0.625mg	Tablets	Medroxyprogesterone 10mg
	Prempak-C	Conj. Estrogen 0.625mg or 1.25mg	Tablets	Norgetresl 0.15mg
	Trisequens	Estradiol 1-2mg + estradiol 1mg	Tablets	Norethisterone 1mg
Quarterly	Tridestra	Estradiol 2mg	Tablets	Medroxyprogesterone 20mg
Continuous therapy	Climense	Estradiol 2mg	Tablets	Norethisterone 0.7mg
	Kliofem	Estradiol 2mg	Tablets	Norethisterone 1mg
	Premique	Conj. Estrogens 0.625mg	Tablets	Medroxyprogesterone 5mg
Gonadomimetic	Livial	-	Tablets	-
Estrogen receptor modulator	Raloxifene	-	Tablets	-

Conj. - Conjugated

Table 2 - Monthly combined non-oral/oral hormone replacement therapy preparations.

Brand	Estrogen	Formulation	Progestogen
Estracombi	Estradiol 50µg	Patches, combipatches	Norethisterone 250µg
Estrapak	Estradiol 50µg	Patches and tablets	Norethisterone 1mg
Evorel-Pak	Estradiol 50µg	Patches and tablets	Norethisterone 1mg
Evorelsequi	Estradiol 50µg	Patches, combipatches	Norethisterone 170µg
Femapak	Estradiol 40µg, 80µg	Patches and tablets	Dyrogesterone 10mg
Nuvelle TS	Estradiol 80µg+50µg	Patches, combipatches	Levonorgestrel 20µg
Evorelconti	Estradiol 50µg	Patches	Norethisterone 170µg

TS - transdermal system

Table 3 - Oral estrogen preparations.

Brand	Estrogen	Formulation	Progestogen
Climaval	Estradiol	Tablets	1, 2mg
Elleste Solo	Estradiol	Tablets	1, 2mg
Harmogen	Estrone	Tablets	0.93mg
Hormonin	Estradiol	-	0.6mg
	Estrone	Tablets	1.4mg
	Estriol	-	0.27mg
Premarin	Conjugated estrogens	Tablets	0.625, 1.25mg
Progynova	Estradiol	Tablets	50, 100µg
Zumenon	Estradiol	Tablets	1, 2mg
Ovestin	Estriol	Tablets	1mg

Local estrogen preparations will provide relief but are often given for too short a time to have an adequate response. Systemic therapy does not always produce an improvement in vaginal symptoms and for women with symptoms of systemic and local estrogen deficiency a combination of systemic and vaginal estrogen may be necessary initially until the vaginal epithelium has responded. For the older woman who does not wish to experience the effects of systemic estrogen, vaginal estrogen using a natural preparation can avoid significant systemic absorption.[57] Once the vaginal epithelium has matured in response to local estrogen, absorption into the circulation occurs more readily.[58,59] The vaginal ring (Estring) that releases estradiol locally over 3 months but with minimal systemic absorption, provides a suitable alternative[60] (**Table 6**).

Bleeding with hormone replacement therapy. Sequential therapy should produce regular and predictable bleeding although a few women will not bleed even though the progestogen has been taken correctly. For many women the bleed is a major cause of dissatisfaction and one of the main reasons for discontinuing HRT. Although bleeding on HRT may be similar to natural menstruation, no more than half of the functional layer of the endometrium is shed;[61] thus medical curettage cannot be an important mechanism by which progestogens protect the endometrium. Instead progestogens influence endometrial morphology by a variety of intracellular biochemical reactions that moderate and attenuate the effects of estrogen.[62] Since there is no physiological need for bleeding, regimens of HRT have been developed to reduce or prevent monthly bleeding and thereby encourage better long term concordance. With the long cycle HRT, the average withdrawal bleed lasts for 5 to 6 days, which is comparable to monthly sequential regimens. However, long cycle HRT is generally associated with a high incidence of breakthrough bleeding. Nevertheless, there appears to be a greater preference to use the quarterly regimen compared with the standard 28 day sequential regimen.[45] The long-term effects of this type of therapy on the endometrium is not yet known. Continuous combined therapy with progestogen everyday is intended to prevent the proliferative effect of estrogen and maintain an atrophic endometrium in order to avoid bleeding. However, studies of various regimens of continuous combined therapy have reported a high incidence of bleeding in the first 3 months, varying from 50 - 80%. This occurs more often in women who are within one year of the menopause than in postmenopausal women. The bleeding is slight and often only spotting, and with time becomes less, so that few women are bleeding after 12 months.[46,47,50] The gonadomimetic hormone tibolone is specifically converted to its D4-metabolite in the endometrium, which has no estrogenic activity, so the endometrium

Table 4 - Non-oral estrogen preparations.

Brand	Estrogen	Formulation	Dose of estrogen
Dermestril	Estradiol	Patches	25, 50, 100µg
Estraderm TTS or MX	Estradiol	Patches	25, 50, 100µg
Evorel	Estradiol	Patches	25, 50, 75, 100µg
Fematrix	Estradiol	Patches	40, 80µg
Femseven	Estradiol	Patches	50µg
Menorest	Estradiol	Patches	37.5, 50, 75µg
Progynova TS	Estradiol	Patches	50, 100µg
Oestrogel	Estradiol	Gel	1.5mg
Sandrena	Estradiol	Gel	0.5, 1mg
Oestradiol	-	-	-
Implant	-	Implant pellet	25, 50, 100µg

TTS - transdermal system, MX - matrix, TS - transdermal system

Table 5 - Progestogen preparations.

Brand	Progestogen	Formulation	Dose of progestogen
Duphaston	Dydrogesterone	Tablets	10mg
Proluton Depot	Hydroxyprogesterone	Injection	250mg/ml
Provera	Medroxyprogesterone	Tablets	2.5mg
Primolut N	Norethisterone	Tablets	5mg
Utovlan	Norethisterone	Tablets	5mg
Micronor	Norethisterone	Tablets	1mg
Crinone	Progesterone	Vaginal gel	45mg/application
Cyclogest	Progesterone	Pessaries	200mg
Gestone	Progesterone	Injection	25mg/ml

Table 6 - Vaginal estrogen preparation.

Brand	Estrogen	Formulation
Estring	Estradiol	Vaginal ring
Ortho Dienoestrol	Dienoestrol	Vaginal cream
Ortho-gynest	Estriol	Pessary
Ovestin	Estriol	Vaginal cream
Premarin	Conjugated estrogens	Vaginal cream
Tampovagan	Stilboestrol	Pessary
Vagifem	Estradiol	Vaginal tablet

is not stimulated.[63] Noncomparative studies with this hormone suggest a low rate of bleeding ranging from 10-15% during the initial months of treatment to approximately 4% after 6 months.[64]

Risk of breast cancer. The view of the Collaborative Group on Hormonal Factors in Breast Cancer is that HRT increases an overall risk of breast cancer.[65] This is particularly so for the continuous unopposed estrogen therapy. However, the increased risk of breast cancer is related to the duration of HRT use and this excess risk disappears within 5 years of stopping the therapy. Women who use HRT for a short time around the menopause have a very low excess risk. Approximately 45 in every 1000 women aged 50 years not using HRT will have breast cancer diagnosed over the next 20 years; in those using HRT for 5 years, this figure rises by 2 extra cases in 1000, in those using HRT for 10 years 6 extra cases in 1000 and in those using HRT for 15 years 12 extra cases in 1000.[66] This data does not provide a reason for women to stop their treatment but does emphasize the importance of breast awareness and regular mammograms.

Risk of endometrial cancer. Unopposed estrogen HRT causes endometrial hyperplasia, which may progress to endometrial carcinoma. The development of endometrial hyperplasia and progression to carcinoma are dependent upon both dose and duration of use. Short duration of use of less than 3 years is not associated with an increased risk, but long term exposure over 3 years is, with a relative risk of 2.7 for Premarin 0.625mg/day and between 3.2 and 4.2 for Premarin 1.25mg/day.[67] Cyclical estrogen/progestogen is now the HRT of choice in women with an intact uterus. Although hyperplasia may still occur there has been no evidence of an increase in the incidence of endometrial carcinoma, in the short term, though a recent report has suggested an increase after 5 years.[68]

Risk of ovarian cancer. Studies on the incidence of ovarian cancer and HRT have been limited by the small number of cases but have in general shown a small increase in the risk of ovarian carcinoma. The relative risk ratio is 1.1 for estrogen users who have had a natural menopause and have used estrogens for 5 years or more.[69] It would be expected that the addition of progestogens in combined HRT would significantly reduce the risk of ovarian carcinoma. Though ovarian cancer in general carries a relatively high mortality, any increase in incidence due to hormone replacement is outweighed by the benefits, including reduction in mortality from ischemic heart disease and other conditions. Nevertheless, all women receiving HRT should have a regular pelvic examination. Pelvic ultrasound examination may be indicated in nulliparous patients and those with a family history of breast cancer or a history of other epithelial tumors including that of breast and cervix.

Risk of venous thromboembolism. Recent studies show an increased risk of deep vein thrombosis and of pulmonary embolism in women taking HRT.[21,22] However, in general the benefits outweigh the risks of treatment for most women with no predisposing factors for venous thromboembolism. In women who have predisposing factors such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, surgery, trauma or prolonged bed-rest, it may be prudent to review the need for HRT as in some cases the risks of HRT may be expected to exceed the benefits.

General guidelines for hormone replacement therapy. For women with a uterus requiring HRT, suitable treatment regimens would be: (i) Pre-menopausal and peri-menopausal – 28 day combined sequential therapy. (ii) Peri and immediate postmenopausal – long cycle or 28 day sequential therapy. (iii) Postmenopausal – continuous combined therapy; tibolone. (iv) Postmenopausal with vaginal symptoms only and not wanting long term hormone replacement – local application of vaginal estrogens. For women without a uterus requiring HRT, suitable treatment regimens would be: (i) Premenopausal with climacteric symptoms – unopposed estrogen. (ii) Postmenopausal – unopposed estrogen.

In conclusion, the wide range of preparations currently available and the relative merits of the different types of hormone and routes of administration mean that it is possible to find a form of HRT to suit most women. Generally, oral therapy using natural estrogen will be the most suitable initial treatment. This is usually cheaper than the transdermal preparations. Quarterly and continuous combined regimens significantly reduce the burden of both the withdrawal bleeds and the premenstrual-like syndrome. The estrogen component of these regimens, however, is identical to the conventional cyclical preparations, and so they do nothing to alleviate the concerns over breast cancer. Tibolone, a synthetic steroid with simultaneous weak estrogenic, androgenic and progestational activity, is a useful alternative. It has been shown to be safe and effective in the treatment of climacteric symptoms without inducing endometrial stimulation. Estrogen receptor modulators such as Raloxifene may be useful in selected postmenopausal women. Continuous clinical contact with patients on HRT is essential so that therapy can be adjusted if necessary; women with problems with their treatment should be referred to specialist menopause clinics. Such clinics can also monitor the long-term effects of HRT on cardiovascular disease and osteoporosis and investigate new treatments, such as the selective estrogen receptor modulators.

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