Hormone Replacement Therapy Part I: Prescribing HRT-Recent Trends

Dr Neerja Goel,Department of Obstetrics & Gynaecology, Guru Teg Bahadur Hospital, Delhi

With the steady increase in life expectancy of women in India (62.5 years), a majority of them survive an age well past the menopause. Presently about 60 million of the population of India are women aged 55 years and over. The menopause constitutes a watershed in a woman's life with average age of reaching it 47.5 years. The postmenopausal period is associated with a significant increase in the incidence of age related health hazards like diabetes and hypertension along with estrogen deprivation effects. In the short term these falling estrogen levels commonly result in a spectrum of unpleasant symptoms such as hot flushes, night sweats, sleep disturbances, vaginal dryness and depression. In the long term absolute estrogen deficiency leads to generalized atrophy of the skin, decrease in lean body mass, an accelerated rate of bone loss from the skeleton producing osteoporosis and a rapid increase in the incidence of coronary heart disease .

Table 1. Acute and Chronic sequelae of menopause

Duration	System	Symptoms/Disease
Acute	Neuroendocrine	Hot flushes, night sweats, insomnia, mood changes, anxiety, irritability, loss of memory and concentration
Menstruation stops	Lower urogenital tract	Genital tract atrophy, dyspareunia, loss of libido, urethral syndrome
Chronic	Arterial Skeletal	Coronary heart disease, thrombosis Osteoporosis

Each of these adverse sequelae could potentially be reversed by Hormone Replacement Therapy (HRT) and the process of aging could be arrested to some extent. Emerging facts are setting new directions favoring HRT for all symptomatic peri and postmenopausal and asymptomatic postmenopausal women. Estrogen remains the mainstay of all treatment protocols. The uncertainty for the universal and liberal prescription of HRT remains in the minds of treating gynaecologists as well as their clients due to many myths and fears. This article aims to present a comprehensive

update regarding the trends of HRT and its rational use. Part I outlines the recent trends in prescribing HRT.

Indications of HRT

Estrogen replacement therapy is indicated for any woman with signs or symptoms of hypoestrogenemia because of the health risks associated with estrogen deficiency. Estrogen replacement should be offered to all postmenopausal women who are not contraindicated. Women with known risk factors for radiovascular disease of osteoporosis should be encouraged to take estrogens to minimize their risks.

Table 2. Recruitment of women for HRT.

Asymptomatic Women:

- Any appropriately aged woman
- Women with a family history or risk of ischaemic heart disease
- Women with a family history or risk of osteoporosis

Symptomatic Women:

- Vasomotor - Hot flushes, night sweats - Palpitations (exclude cardiac pathology)
- Atrophic - Vaginal dryness, urinary symptoms, recurrent urogenital infection
- Collagen related - Muscle and joint pains
- Other symptoms - Psychological and emotional in the presence/ Absence of established psychiatric illness.
- Following bilateral salpingo-oophorectoma
- Premature ovarian failure
- Gonadal dysgenesis
- Antigonadotrophin therapy

Contraindications

As with all treatment, HRT requires consideration of the severity of illness to be treated and the possible side effects. Absolute contraindications are few but most workers would consider abnormal vaginal bleeding, current endometrial and breast cancers as contraindications. The reports on long term use of HRT with the recurrence of breast cancer are controversial1. However, long term use (>10 years) and high doses of estrogens have been implicated in increasing relative risk. The actual survival rate is reported to be rather increased in women on HRT because of regular follow up and detection at an earlier stage. The addition of progestogens seems to be of no benefit as regards protection against breast cancer, indeed there have been suggestions that the

opposite might be the case2.

Table 3a. Contraindications of HRT

Absolute contraindications

- Acute endometrial/breast cancer
- Acute phase myocardial infarction
- Pregnancy
- Undiagnosed breast lump
- Undiagnosed abnormal vaginal bleeding

Other contraindications

- Primary cerebrovascular accidents
- Acute phase pulmonary embolism and DVT
- Inherent abnormalities of coagulation
  - anti-thrombin III
  - Fibrinogen and platelets
  - Protein C&S

Most of the contraindications (Table 3a) do not apply as they are extrapolations of oral contraceptive data and while hypertension, previous/present ischaemic heart disease or coronary thrombosis are contraindications for oral contraceptive pill, they are indications for HRT. However, hypertension and diabetes must be controlled before HRT is prescribed.

A past history of venous thrombo-embolism if occurred in association with an obvious precipitant such as pregnancy or post partum should not be regarded as a contraindication. In the case of idiopathic, recurrent or in the presence of strong family history, a screen for a prothrombotic state should be undertaken and should be treated accordingly before prescribing HRT (Table 3b, 3c).

Table 3b. Conditions which require precautions while prescribing HRT

- Fibroid - 6 monthly follow up
- Endometriosis - estrogen only if completely excised, otherwise follow up
- Gallstone - non oral preferable
- Hepatobiliary problems - not worsened by non-oral HRT
- Antiepileptic therapy - non oral HRT does not interfere
- Thrombosis with a recognized high risk factor
  - Post partum
  - Post trauma

- Post-operative, particularly pelvic surgery
- Thromboembolism in pregnancy (Transdermal route has less effect on clotting factors)

- Pre-operative period - No need to stop HRT, unless positive history of spontaneous thrombosis is present

Table 3c. No contraindication to HRT

- Obesity, heavy smoker, diabetes, migraine
- Migraine, mental depression, otosclerosis
- Varicose veins, superficial thrombophlebitis
- Abnormal cervical smear, cancer cervix, cancer ovary, non-estrogen dependent cancers, malignant melanoma, Benign breast disease

Principles of estrogen metabolism

The primary source of estrogen in reproductive years is pre-ovulatory follicle and corpus luteum and estradiol (E2) level ranges from 40 pg/ml to 250 pg/ml. At menopause, E2 levels drop to less than 20 pg/ml and the predominant circulating plasma estrogen change from E2 to estrone (E1), which is a weaker estrogen. Thus, the plasma E2:E1 ratio shows a marked fall to 0.42 compared to 1.9 at ovulation in young females. The effect of estrogen on various tissues depends on the number of estrogen receptors and nuclear retention time. E2 being most potent has the longest retention time (6-24).

Weaker estrogens such as E1 and estril (E3) have a retention time of only 1-4 hours. Throughout the body, estradiol is converted to estrone, which is bound partially to sex hormone binding globulin (SHBG), which is synthesized in liver. The unbound lipophilic molecule of E2 diffuses passively into the cells with estrogen receptors there by exhibiting its action. While considering estrogen replacement for any patient, it is important to consider the goals of therapy and the target tissue.

The amount of estrogen required to treat genitourinary symptoms in much less than the amount needed to eliminate vasomotor flush specially after bilateral oophorectomy in young women and to prevent osteoporosis and ischaemic heart disease in older women. The optimum serum estradiol levels are 40-60 pg/ml, which can be achieved with various estrogen preparations (Table 4).

Table 4. Estrogen formulations and drug serum levels

Formulation	Dose (mg)	Serum level estradiol (pg/ml)

1. Conjugated equine estrogen	0.625 1.25	40 60
2. Micronized estradiol	1 2	40 60
3. Transdermal estradiol patch	0.05 0.10	25-40 60
4. Estradiol Valerate	1	50
5. Estradiol gel	1	40-50

Preparations and routes of Estrogens and Progestogens

Oral estrogens

The oral route of administration of estrogen is used most commonly. Because native steroids are relatively water insoluble, modifications of estrogens for oral delivery includes conjugated estrone sulphate, estradiol valerate, conjugated equine estrogen, micronized estradiol and synthetic molecules (17 ethinyl estradiol, quinestrol and diethylstilbestrol).

Conjugated equine estrogen (CEE) has been available for nearly 4-5 decades. It is prepared from the urine of pregnant mares and is composed of 50-60 per cent estrone sulphate with equine estrogen such as equilin and 17(-dihydroequilin. CEE is absorbed with peak level of 4 hours and half-life of 12-14 hours. The gastro-intestinal tract preferentially converts E2 to E1 and the portal venous system rapidly transfers the entire steroid in the form of 'bolus' into the hepatic tissue before systemic circulation where it is metabolized to estrone and estrone 3 – glucoronide.

This is called the 'first pass' effect. Because of the first-pass effect, oral estrogen has to be given at a much higher dose reducing the systemic bioavailability to 2-10 per cent.

The metabolic and beneficial consequences of hepatic first pass lead to increased synthesis of 'estrogen-sensitive' proteins such as apolipoprotein A, higher density lipoprotein, sex hormone – binding globulin, transferrin, ceruloplasmin, thyroxine – binding globulin, and other factors beneficial for CVS effects whereas the risk of venous and arterial thrombosis and hypertension may be increased due to increase in renin substrate. CEE has more potent hepatic effect than other oral preparations.

Synthetic molecules such as 17-ethinyl estradiol and diethyestilbestrol have an enhanced hepatic potency and extended biological half-life, this may lead to increased risk of thromboembolism and other metabolic derangement, and thus it is never recommended in HRT formulations. Induction of hepatic enzyme by phenytoin group of drugs, rapid estrogen inactivation occurs thus reducing the drug level. Micronization of estradiol results in good systemic levels, which is only seen by oral route not when micronized estradiol is administered vaginally or by transdermal application.

Transdermal Estrogens

Estrogen delivery by transdermal therapeutic system (TTS) represents an important advance in the evolution of hormone replacement therapy. It has basic advantage of being non-oral and higher safety profile. This also partly lacks first pass liver metabolism, which is protective against metabolic derangement. The main advantage of this route is that pure estradiol can directly be administered to the systemic circulation through adequate absorption of estrogen by skin and thus the therapeutic serum levels of estradiol is maintained and ratio of E2:E1 is not altered. TTS estrogen was first marketed as a membrane patch of 5 layers with a size and thickness of 18 cm^2 and 5 mm respectively. The drug content was 4 mg of micronised 17 β estradiol in an alcohol gel. It had a major disadvantage of local skin reaction due to presence of alcohol. The second generation patch, which is currently available as matrix patch is of 0.1 mm thickness and a size of 16 cm^2 and the drug is delivered from the adhesive layer rather than ethanol base and hence is better tolerated with minimal local reaction. An important disadvantage of matrix patch is that it cannot be re-applied after being taken off so it is not to be taken off before bathing.

The patch is applied twice a week away from breast, preferably on the shaved skin of buttock, thigh or legs. Storage at 25°C and air drying for 15 seconds has been reported to reduce skin reactions. Exposure to sunlight should be avoided and oral estrogen should be stopped 1 week prior to application of patch. After 4 hrs of administration the serum estradiol rises from 15 to 40-50 pgml [3,4]. By avoiding hepatic first pass the major advantage of transdermal estrogen is that it lowers triglycerides and hence can be given in hypertriglyceridaemia. It does not have much effect on HDL and LDL.

Transdermal Gel

Compliance with Estraderm matrix patch is reduced because of skin problems and drop out rate upto 8 per cent has been reported. In order to increase the continuity rate, transdermal hydroalcoholic non-occlusive estradiol gel is introduced. The gel contains 0.06% w/w 17 β estradiol. A measured dose of 0.75 mg estradiol is dispensed and the usual recommended starting dose is two measures daily applied on a large area of arms and legs. The progestational agents are added like any other method of estrogen therapy. E1:E2 ratio of 1 is achieved confirming its physiological delivery. Absorption is rapid and effective levels are obtained which provides symptomatic relief comparable to oral estrogen [5].

Vaginal route

Vaginal absorption of estrogens has been used widely, most popularly for the treatment of atrophic vaginitis and other urogenital symptoms. Estriol cream is prescribed in patients with significant urogenital symptoms and as a preoperative therapy for elderly patients undergoing vaginal surgery. Vaginal route is advocated in those patients especially in geriatric population with psychosomatic problems where other routes are contraindicated. A 15 gm pack of estriol succinate is available in India and one

application daily of 0.5 gm delivering 0.5 mg of estriol base is advocated for three weeks and twice weekly for three to four months. Progestin supplementation is not required because of very short nuclear retention time.

Subdermal Implants

Pellets of crystalloid estradiol have been used as subcutaneous implants in a dose of 50 mg at six monthly intervals, which produces serum level of nearly 40-60 pg/ml of estradiol. It is defined as most physiologic form of drug delivery offering symptomatic relief and preventive therapy for cardiac disease and osteoporosis [6]. However supraphysiological blood levels and tachyphylaxis may be seen if the drug is given too frequently [7].

At times, prolonged endometrial proliferation may continue after discontinuing the implant for which progestins are required for one to two years after stoppage of therapy [8]. The lower dose of 25 mg is a useful alternative for older postmenopausal women. Testosterone in a 100 mg pellet can also be given along with estrogen if unsatisfactory response is reported. This combination is useful for treatment of depression, lethargy, loss of libido and reduced sexual response. In India, it is not yet used routinely in clinical practice.

New delivery system of Estrogens

Continuous low dose estradiol releasing vaginal ring

This delivery system offers an adequate symptom control by local ultra-low dose therapy while avoiding the potential for systemic absorption. This system utilizes a soft and flexible silicone ring, 55 mm in overall diameter with a 9 mm cross-sectional diameter. The silicone core acts as a drug reservoir and contains 2 mg of micronized 17β-estradiol. There is uniform sustained release of estradiol (5-10 microg/24).

In a study, 194 postmenopausal women were instructed to insert the vaginal ring high up in vagina with instructions for the ring to remain *in situ* after obtaining a negative progesterone challenge test (Medroxy progesterone acetate 5mg daily for 12 days). All patients were evaluated for relief of symptoms like vaginal dryness, dyspareunia, dysuria and/or urgency and pruritis. Atrophic signs included pallor, petechiae, friability or dryness. Vaginal pH and vaginal mucosal maturation were also studied.

The symptom response after 12 weeks varied from 66-90 per cent for various symptoms. Atrophic changes also improved (40-70%). Vaginal pH fell from 6.3 to 4.6 after 12 weeks and maturation of estrogen dependent cells rose from 25 to 59. The vaginal ring response was compared to CEE creams and there was no statistically significant difference in various parameters [9]. Thus vaginal ring is easy to use and the compliance rate is high.

Progestogens

The clinical use of progestins during menopause is to oppose the estrogenic effects on the endometrium. Progestins decrease estrogen receptors and mitotic activity and develop the stromal component of the endometrium. This prepares the endometrium for future prostaglandin and helps the uniform endometrial shedding. Progestins can be used in two regimens. These can be added cyclically (12-14 days a month) to convert proliferative endometrium to secretory or alternatively given continuously with estrogen throughout the cycle to prevent the proliferation and induce atrophy of endometrium.

Oral progestins used widely for menopausal therapy include three distinct categories a) Natural progestogens, b) the 19–norprogestins and c) C-21 compounds (Table 5). Natural progestins are usually not used for HRT because they induce drowsiness and other side effects. Medroxy progesterone acetate has properties close to its native compound. This compound has increased progestational effects and oral efficacy.

Table 5. Progestins in HRT regimen

Generic name	Brand name	Sequential Doses	Combined
Synthetic 19 Nortestosterone derivative- Norethisterone	Regesterone	2.5mg	1mg
Synthetic C-21 Progesterone derivative Modus ie Medroxyprogesterone acetate	Meprate Farlutal Deviry Provera	5-10mg	2.5mg
Dydrogesterone	Duphaston	1-20mg	
Desogestrel	Neogest	150 mg	

The use of 19–norprogestins has become minimized as this compound has androgenic properties and adverse effects on lipoproteins. The dose chosen should be lowest ie 2.5 mg of norethisterone and 150 microg of norgestral for 12 days every month.

The clinical trial on alternative progestins like desogestral, gestodene and norgestimate are ongoing as this compound has excellent bioavailability and minimum effect on lipoproteins.

Dydrogesterone, the spatial isomer of 6-dehydroprogesterone, is a potent compound devoid of androgenic or estrogenic properties. It does not oppose the potentially beneficial effects of oral and transdermal estrogens on lipoproteins [13]. It also maintains the glucose homeostasis and lowers insulin resistance [14]. A dose of 10-20 mg for 10-14 days per month protects postmenopausal endometrium and gives an effective cycle control with few side effects [15].

Pretreatment evaluation

All patients who are candidates for hormone replacement therapy should be thoroughly evaluated by means of detailed medical history and a complete physical examination both for proper diagnosis and to search for contraindications.

Full history includes personal, social, obstetric, gynecological, menstrual and sexual; previous medical therapy or surgical interventions (diabetes, hypertension jaundice, gall stones, liver disease and thrombosis), menopausal symptoms, psychiatric problem, skeletal, psychomotor symptoms and cognitive performance. A physical examination includes height, weight, obesity index, blood pressure, breast, abdomen, and pelvic and rectal examination.

Baseline investigations required are hemogram, urinalysis, fasting lipid profile, blood sugar, ECG, pap smear, ultrasound (endometrial thickness and ovarian volume) mammography (once in 2 to 3 years and annually after 50 years). Serum estradiol in asymptomatic postmenopausal women and serum FSH and LH in women with premature menopause are recommended for proper monitoring of dose of HRT. Endometrial sampling is not required in routine practice but if there is abnormal bleeding before or during HRT, hysteroscopy/curettage is advised.

Regimens

The consensus of current opinion is that single therapy with estrogens is advisable for hysterectomized women and combined therapy with estrogens and progestogens for all women with an intact uterus in view of endometrial protection by opposing the mitotically stimulatory action of estrogen. Several methods are available for adding progestogens to estrogen replacement suitable for menopausal symptoms (Table 6).

The method preferred for new patients is the cyclic sequential. This has few side effects except for withdrawal bleeding seen in 97 per cent of patients. In perimenopausal symptomatic women, it is advised to time addition of progestogen so that last tablet is taken before first day of the next anticipated period. Thus, with a 25-day cycle tablet is taken from day 13 to day 25 and in 45 days cycle from day 33 to day 45.

Table 6. Regimes of addition of progestogen in HRT.

Regime	Estrogen	Progestogen
Cyclic Sequential	1st - 25th/month	13th - 25th/month
Continuous Sequential	Every day	1st - 14th/month
Continuous Combined	Every day	Every day
Cyclic Combined	1st - 25th/month	1st - 25th/month

Appearance of symptoms in estrogen free period necessitates to switch on to continuous

sequential regimen. Progestogens are added for the first 12-14 days of each calendar month with continuous delivery of estrogen. For women objecting to resumption or continuation of menstruation, continuous or cyclic combined regimen has been advised. The choice and dose of progestogens is dependent on the regimens used. Dydrogesterone (Duphaston) 10-20 mg, medroxy progesterone acetate 5-10 mg and norethindrone 2.5 mg is recommended in sequential regimen and for continuous combined regimen, the dose of MPA is reduced to 2.5 mg and norethindrone to 1 mg. In cyclical combined the advantage of regular spotting on day 26 or day 27 is preferred to continuous combined where there could be breakthrough bleeding in the cycle. Moreover, in cyclic combined regimen 75 per cent of patients will become amenorrheic within 4 months.

Long cycle HRT

Longer sequential cycles ranging from three to six months have been evaluated. Since endometrial hyperplasia has been found after four months, three months may be the longest length of cycle that is safe [16,17]. A seventy-day course of 2 mg estradiol valerate or 0.625 mg CEE is given orally followed by 20mg medroxy progesterone acetate daily for 14 days. Placebo tablets on days 85-90 are administered to complete the course of 3 months. Withdrawal bleeding for 5-6 days, which is comparable to monthly continuous sequential regimen, occurs. The incidence of endometrial hyperplasia is comparable to all other regimens [18].

Novel bleed free regimen

A regimen of continuous estrogens and interrupted progestogens is believed to increase receptors during the estrogen only phase, making the endometrium sensitive to subsequent estrogen and progestogen activity, and down regulate both receptors during exposure to the progestogen limiting the endometrial growth. In a pilot study, each week estrogen patches (releasing 50 μ g of estradiol and 250 μg norethisterone acetate per day) for three days. After the end of three applications endometrial proliferation, both by ultrasound and histology did not reveal any endometrial proliferation. The maximum endometrial thickness was found to be 2.8-3 mm and histology revealed atrophic, secretory or proliferative endometrium. Amenorrhoea was reported in 10 out of 14 patients at the end of three months [19].

Tibolone

Tibolone [(7α, 17α)–17 hydroxy–7 methyl–19-norpregn 5(10)-en-20-yn-3-one] is a synthetic steroid with weak estrogenic, progestogenic and androgenic properties and the code name is OrgOD14. Comparative animal studies have demonstrated that tibolones' estrogenic potency is about one-fiftieth that of ethinyl estradiol, its progestogenic potency is one-eighth that of norethisterone and its androgenic potency is one-third that of norethisterone [20]. Clinical efficacy studies have demonstrated that the appropriate dose is 2.5 mg per day. The drug is rapidly absorbed after oral administration, peak value reaches after 1.5 – 4 hours and half-life is 30-45 hours. The development of this

unique gonadomimetic steroid has offered almost a complete therapy of climacteric complaints whilst, at the same time avoiding the problems associated with classical HRT ie absence of withdrawal bleeding.

Effects on urogenital system include restoring a healthy vaginal environment, reducing dyspareunia and vaginal infections after 3-5 weeks of starting therapy in nearly 95-99 per cent of patients [21]. Tibolone and its metabolites have a high progestogen receptor binding affinity on endometrium. This mechanism may therefore provide an explanation for the weak stimulatory effect on endometrium and decreased incidence of vaginal bleeding. However, vaginal break-through bleeding does occur during treatment with tibolone if any endometrial proliferation is already present due to estrogen usage in recent past. Histology of endometrium after 2 years of use reveal occasional proliferation but no new case of hyperplasia has been observed [22].

Unlike estrogens, tibolone does not alter HDL – cholesterol and LDL – cholesterol. Total cholesterol values remain either unchanged or tend to decrease but triglycerides levels have been shown to decrease significantly in women over 50 years. The reduction of triglycerides may constitute an advantage over oral estrogen in cardio protective effect.

In a two-year study the effect of 2.5 mg tibolone taken every day in recently menopausal women revealed an increase in bone mass by 2.5 per cent in the spine and 3.5 per cent in neck of femur [23]. Post hysterectomy bone loss has been reported to accelerate at least during the first year of surgery. The efficacy of tibolone was assessed in a 1-year placebo controlled study in 25 women and it was found that bone density remained unchanged in tibolone treated group as compared to the placebo treated. However, there was a 6.12 - 12.4 per cent bone loss in radial shafts measured at 6 months and 12 months after hysterectomy and bilateral salpingo-oophorectomy [24].

The major side effects of tibolone were weight gain and/or a tendency to bloating or edema in 11.28 per cent of women, breast tenderness and breast enlargement in 7.52 per cent, gastrointestinal symptoms in 5.26 per cent and vaginal bleeding in 12.69 per cent.

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