Pharmacology of Estrogen in Gyaecological Practice

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The natural estrogens cannot be used for may pharmacological applications, particularly for contraceptive use, for the simple reason that some of them are not orally effective. On the contrary synthetic estrogens are more effective at a lower concentration and can be administred orally as well (Table 1.)

Table 1
Classification of Estrogens

1. Natural estrogens
   - Estradiol
   - Estrone
   - Estriol

2. Conjugated steroidal estrogens
   - Estrone sulphate
   - Estradiol valerate
   - Estradiol benzoate
   - Estriol succinate or hemisuccinate

3. Nonconjugated steroidal estrogens
   - 17 α-ethinyl estroadiol
   - Mestranol

4. Sythetic nonsteroidal estrogens
   - Stilbestrol
   - Clomiphene citrate
   - Tomoxifen

Natural estrogens:

Estradiol is the most important natural estrogen and is secreted from ovary. It is not effective orally and hence as such has no therapeutic application. Micronized estradiol preparations are orally active, and have been described for menopausal HRT. And conjugated varieties such as estradiol benzoate and estradiol valerate are used therapeutially for providing estrogen support in fertility disorders. The conjugated steroidal estrogens, namely estrone sulphate (Premarin) is employed as oral estrogen preparation for menopausal HRT.

Estriol succinate, available as 1 mg tablets (Evalon) is employed for the senile subjects (past 60 years) who need just the lowest concentration of estrogen to take care of the senile vaginal and urethral changes, but not sufficiently higher levels to produce endometrial response and bleeding.

Estriol succinate is a weak estrogen compared to the other compounds. Hence it has its specific application in climacteric, when subjects past 60 years complain of problems related to senile vaginitis and urethritis. A small dose of estrogen, in the form of evalon 2 to 4 mg/day will be enough just to take care of the genitourinary problem, at which dose endometrial stimulation does not occur. Hence there will be no need for progestogen supplementation. Alternately, estriol vaginal cream is available for local vaginal application. However, in a dose of 8 to 12 mg / day given in divided doses, this drug could take care of bone metabolism in the menopausal subject, but then progestogen administration will be mandated since endometrial proliferation occurs at this dose range.

Ethinyl Estradiol:

Currently ethinyl estradiol in lowest possible dose has emerged as the most sought after estrogen for menopausal hormone replacement therapy (HRT). Its contraceptive role is well acclaimed. This nonconjugated steroidal estrogen, namely, ethinyl estradiol is the only estrogen employed in the low dose estrogen progestogen oral contraceptive pills. The naturally occurring 18 carbon atom 17β-estradiol which is orally inactive is converted to the orally active form, namely 17α-ethinyl estradiol, by the addition of ethinyl radical to the 17th α position. Addition of ethinyl radial at 17th α position of any compound enhances the potency of the parent compound, be it an estrogen or progestogen. Thus ethinyl estradiol is very effective orally and at a very low dose exerts antifertility effects. The current recommended dose of the agent in

OC pill is as low as 20 µg.

Ethinyl estradiol at a dose of 6 to 10µg is as effectie as 0.625 to 1.30 mgs of conjugated estrogen with estrone sulphate 40% (premarin). In this low dose of 6 to 10µg ethinyl estradiol is more effective for HRT (particularly in cardioprotection) than premarin and is as safe as Premarin. The standard dose of ethinyl estradiol employed in OC combination is 30mg. The progestins used in this OC combinations are norgestrel, norethisterone or norethisterone acetate. However, recently it has been observed that at a dose of 20 µg ethinyl estradiol, with 150 µg of desogestrel, is able to exert ovulation inhibition, good cycle control and provide all the antifertility. effects, and hence at this dose it is an effective contraceptive. By reducing the dose of ethinyl estradiol to 20 or 10 µg, the only setback of this agent, namely, coagulation disorder is also practically negated, and currently this concentration is hence favoured for menopausal HRT even in high risk subjects.

Dose equations of various estrogens (Table II):

In the following doses the various estrogenic preparations exhibit identical potency (Table II):

Tabe I I

Estriol	12 mg
Estradiol	5 mg
Stilbesterol	5 mg
Premarin	3.75 mg
Mestranol	0.08 mg
Ethinyl estradiol	0.05 mg

At doses of 10 µg/day of ethinyl estradiol or 1.25 mg/day of premarin serum estradiol levels have been shown to rise into the premenopausal early follicular range of 40 to 60 pg/ml at 24 hours after the first dose, and revert vaginal cytology to premenopausal state. Furthermore, they have been conclusively shown to reduce postmenopausal bone loss in the above mentioned doses. At a dose of 0.3 mg of premarin or 6µg hepatic protein synthesis could be initiated.

Transdermal estrogen administration:

Parenteral delivery of estradiol via a transdermal therapeutic system (TTS) as patch or gel appears to overcome many of the pitfalls noted with other modes of non-oral estrogen replacement. The general benefits include: such attributes as maintenance of a relatively constant drug level within the circulation, lower overall drug dose, and reduced frequency of drug dosing, and ease of termination of drug delivery by removal of the system. Additionally, the system is designed so as to control the rate of drug delivery and to minimize variable absorption between patients because of skin differences, such as color or hydration.

The 0.05 mg/day patch is rounded and has a surface area of 10^2, and contains 4 mg of estradiol dissolved in ethanol. In this formulation estradiol is delivered at a constant rate of 0.05 mg/day over 3 or 4 days of suggested use, after whch time the rate of drug delivery greatly declines. One of the possible explanation for the abrupt drop in estradiol delivery after a 3 to 4 day period may be the absorption and / or evaporation of the vehicle, namely, ethanol.

For patients who are extremely sensitive to daily fluctuations in systemic estrogen levels, the transdermal system can deliver stable levels of serum estradiol during the first 2 days after application. The currently available formulation must be changed twice weekly, one patch lasts 3 days and the other for 4 days, and the estradiol levels begin to drop after 2 days. This may not be significant for most women, but some women experience increased vasomotor flushes on the third and fourth day of patch use. The addition of ethanol to the patch at the point in the patch life-time when the rate of estradiol delivery is starting to decline enables the patch to continue release of estradiol. It has been advocated to inject 0.6 ml of ethanol into the patch on the third day to prolong the estrogen delivery of the pack for a total of one week.

Hormonal contraception:

Hormonal contraception employing low dose estrogen

and progestin combination has been the most popular, effective and reversible method of fertility control. The aim of prescribing low dose estrogen-progestin combination (OC pill) is to provide health care measure for women of the reproductive and nonreproductive age group with accent on improving the quality of life. The vivid description on steroidal chemistry and their pharmacological application throws light on the usually untouched basics of contraceptive therapy. During the 1960's the OCs in use contained upto 150 µg of ethinyl estradiol (EE), during the 1970's most contained 50 µg, while the most widely used OCs during the 1980's contained only about 30 µg. it seems likely that the 1990's will be the decade of the 20 µg EE pill. The currently available ultra low dose estrogen progestin combination hormonal contraceptive pills are a boon for properly selected women, both for contraception and various noncontraceptive benefits.

The progestins employed in the commonly available OCs are norethisterone, norethisterone acetate, lynestrenol and norgestrel. These agents effect optimal fertility control only in combination with 30 µg EE. However, the newer gonane progestin, namely, desogestrel in a dose of 150 µg can achieve fertility control and cycle control even with 20µg EE. Moreover desogestrel complements many of the beneficial effects of EE, so much so, it is more of an antiandrogen. Hence the best OC pill of choice could be combination of low dose desogestrel (150µg) and ethinyl estradiol (20 µg). This newer combination has tremendous noncontraceptive benefits for the patients extending from menarche to menopause. They include cycle control, treatment of acne and hirsutism, control of PMS, oncological protection against endometrium, ovary and benign breast diseases, and estrogen support after the age of 35 years. Current data do not support a higher incidence of breast cancer to OCs.

Cardioprotection by estrogen:

Estrogen is protective against cardiovascular diseases in women. In the active reproductive age the endogenous estrogen offers this protection. However, from the time of ovarian decline, starting as early as 35 to 40 years, we find that pharmacological estrogens offer more protection than the endogenous estrogens. Probably the declining endogenous estrogen may be one reason. But more important is the effect on HDL and LDL cholesterol. Endogenous estrogen certainly lowers the level of LDL cholesterol and leaves HDL cholesterol unaffected. Whereas pharmacological estrogens, particularly ethinyl estradiol, apart from lowering the level of LDL cholesterol increases the level of HDL cholesterol. This supraphysiological increase in HDL cholesterol, which is seen only in therapeutic application of estrogen (and not in endogenous estrogen), is the most cardinal cardioprotective effect of lipid metabolism.

Whereas only 25 to 50% of cardioprotection is offered by the "lipid friendly" actions of estrogens, the remaining 50 to 75% of cardioprotection is provided by the direct vascular effects of estrogens. It has been of late observed that ethinylestradiol has a very potent cardioprotective effect as against other estrogens, while causing no altered coagulation at low concentrations. There are atleast 19 following various cardioprotective metabolic effects of estrogen:

Increase in sex hormone binding globulin (SHBG):

This effect favors binding of free testosterone and lowering of androgenic function. The lower androgenic function favors cardioprotection through the "lipid friendly" mechanism.

There are three groups of progestins that are combined with estrogen to offer endometrial protection which include: 1. Duphaston or medroxyprogesterone acetate; 2. Norsteroids including the gonane norgestrel; and 3. newer gonane, namely, desogestrel.

The first group does not interfere with the beneficial effect of estrogen on SHBG, the second group reverses the beneficial effect, whereas desogestrel potentiates or augments the beneficial effects by 3 to 4 times. Thus the choice of progestin should be group 1 or 3, and not group 2.

"Lipid-Friendly" effects, particularly increase in HDL-C:

While endogenous estrogen promotes lowering of LDL-C only pharmacological estrogens offer supraphysiological elevation of HDL-C which is the key factor in cardioprotection. Particularly, ethinyl estradiol is the most potent and the next is conjugated estrogen in elevation of HDL-C. The marginal increase in triglycerides caused by ethinyl estradiol is currently not considered as a risk factor for heart disease.

Many 19-nor steroids lower HDL Cholesterol whereas duphaston and medroxyprogesterone acetate do not have any ill effects on HDL, and this finding may affect the frequency of their use. The newer gonane progestin, desogestrel, however, is "lipid-friendly" and favours increase in HDL-C. Thus, combination of low dose ethinyl estradiol and desogestrel favourably alters the lipid metabolism and remains cardioprotective.

Estrogen as scavenger for oxygen free radicals:

Estrogen is an antioxidant which is effective in scavenging the free radicals and preventing them from lipid peroxidation and inhibit accumulation of oxidized LDL particles within the vascular wall. This effect is most pronounced with ethinyl estradiol than any other estrogen. The progestins do not reverse this antioxidant effect of estrogen.

Inhibition of lipid peroxidation:

Oxidatively modified LDL induces monocyte recruitment, retention in the subendothelial space, and transformation into foam cells, in addition, lipid peroxidation products may be directly cytotoxic to endothelial cells, leading to intimal injury and necrosis and subsequent smooth muscle cell proliferation. Moreover, oxidatively modified LDL has been detected in atherosclerotic lesions.

Ethinyl estradiol is an effective free radical scavenger and could inhibit lipid peroxidation. Equine estrogens, premarin, is more potent antioxidant than estrone or estradiol. Progestins do not have any antioxidant properties.

Improved Nitric Oxide (NO) metabolism:

Nitric oxide is produced by the vascular endothelium which mediates the vascular relaxation function of various endothelium dependent vasodilators such as acetylcholine, and bradykinin. Estrogens influence the release of NO from vascular endothelium, and thus indirectly is vaso-depressive. Nitric oxide levels decline in menopausal subjects and is improved by estrogen therapy.

The primary pathway of ethinyl estradiol is the strong direct effect on the intima of arteries that may act as oxygen free radical scavenger and vasodilator. Thus ethinyl estradiol has been proved most effective estrogen on vascular effect mediating cardiac protection.

It is speculated that the beneficial effect of estrogen on NO may be partly reversed by progestogens such as norethisterone acetate. However, other progestins such as duphaston or desogestrel should not reverse the estrogenic benefits on NO.

Improved insulin sensitivity and decline in insulin levels:

Elevated plasma insulin and glucose intolerance both have been risk factors in the pathogenesis of cardiovascular disease. Estrogen has been associated with enhanced insulin sensitivity, increased insulin clearance, as well as decreased fasting insulin levels. All degrees of glucose intolerance have been linked with arterial hypertension, dyslipoproteinemia, and microvascular disease. All of these conditions appear to be related to the basic problem of insulin resistance and are clearly linked to increased morbidity and mortality from cardiovascular disease.

Estrogen binds to specific sites on the insulin receptors and prevents degradation of insulin molecule. This action promotes insulin biologic activity and will explain how estrogen actually improves carbohydrate metabolism and remains cardioprotective in this respect. Conjugated estrogens may improve insulin sensitivity at a dose of 0.625 mg and progestins may attenuate this positive effect.

Progesterone and progestins impair carbohydrate metabo-

lism, the impact of which appears to be related to potency, dose and duration of treatment. This adverse effect is due to interference with hepatic insulin receptor binding, which results in decreased heatic uptake of insulin.

The levonorgestrel was shown to have the worst effect, followed by norethisterone. The impact was mildest for desogestrel after 6 months and after one year, although the changes were within normal limits for healthy women. Hence by employing the desogestrel-ethinyl estradiol combination the impact on glucose and insulin metabolism could be minimized and that of lipid metabolism improved, a desirable metabolic balance in terms of improved health care measure.

Reduction in blood pressure:

Oral estrogen administrtion increases renin substrate (angiotensinogen). These changes are not observed with transdermal administration. Despite an increase in angiotensinogen, hypertension has not been associated with the use of oral estrogens in clinical studies. It is due to the fact that mean activity of angiotensin converting enzyme (ACE) is decreased by 20%. The sum effect is slight reduction in blood pressure, and hence low dose estrogens, ethinyl estradiol (10-20μg) or premarin (0.625 mg) can be employed safely even in mild benign hypertensive subjects under strict medical supervision. No progestins have been found to reverse this estrogenic benefit on blood pressure.

Improvement in water and electrolyte metabolism:

Estrogen is also associated with a compensatory significant reduction of plasma renin and pro-renin concentrations, suggesting OC-induced decreased secretion of these agents by the kidney. In addition progestins may cause water retention, but also has been shown to possess natriuretic effect (antialdosterone properties). Thus, ultimately there is no proof of water retention or loss during OC use.

Decreased risk of Thrombogenesis and improved fibrinolysis:

Thrombogenesis plays an important role in the pathogenesis and presentation of coronary heart disease, and hemostatic factors are important. Menopause has a variety of effects on hemostasis, including increased levels of procoagulant factor VII, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1). This denotes an increased risk of arterial thrombosis attributable to hypercoagulability in postmenopausal women.

Fibrinolytic activity :

Subjects with a high estrogen status (premenopausal subjects and postmenopausal subjects on HRT) have greater fibrinolytic potential (low PAI-1) than those with low estrogen status (men and postmenopausal women without HRT). Thus we understand that estrogenic status is associated with fibrinolytic potential.

Venous thrombosis:

There is still controversy on the effect of HRT on venous thrombosis. Epidemiologic studies have not demonstrated a positive association between estrogen HRT and venous thrombosis or thromboembolism, even in women at risk for thrombosis such as diabetics or hypertensives described a significant decrease in antithrombin III after 12 months of transdermal estradiol, or equine conjugated estrogen treatments. In other studies either antithrombin III is unaffected after 3-6 months or there is a significant increase of antithrombin III.

Postmenopausal subjects on estrogen therapy returned protein S and C to their original levels after 3 to 6 months of treatment even though this is to be proved by long term studies. Overall, estrogens by current informations appears beneficial to the cardiovascular system by inducing fibrinolytic activity as well as progressively reducing coagulation activity. The progestins do not alter these favourable effects.

Prevention of platelets aggregation:

The role of platelets in the process of atherosclerotic cardiovascular disease is well established. There has been

significant decrease in adrenaline-induced platlelet aggregation and ATP release after 3 months of use of conjugated estrogen. However, this change is not significant for patients receiving combination pill or progestogens alone. Thus it is evident that estrogen replacement therapy has antiaggregation effect on platelets, and this needs a long-term study.

Decrease in endothelin -I:

Endothelin-I produced by human vascular endothelium is the most potent vasoconstrictor of coronary arteries as yet discovered. In addition, endothelin-I can play a key role in myocardial infarction. In the report of Ylikorkala et al and Chen et al., it has been observed that endothelin-I was significantly decreased at 6 and 12 months of use of estrogens. Moreover, progestogens, including nor-steroids did not interfere with this beneficial effect. Thus, the current data suggest that the protective effect of HRT against cardiovascular disease may in part be attributable to the suppression of endothelin-1 production.

Decrease in homocysteine concentration:

Homocysteine has been found to be another important risk factor for cardiovascular disease independent of plasma lipid profile. Arteriosclerotic changes related to elevated homocysteine concentrations have been suggested to be induced by increased lipid peroxidation due to reactive oxygen generation by homocysteine. Its reported increase after menopause has been suggested to explain part of the increased risk of developing cardiac disease in postmenopausal subjects. The recently published data on decreased homocysteine levels during HRT may indeed partially account for the decreased risk of heart disease in postmenopausal HRT.

Postmenopausal ethinyl estradiol and duphaston administration for 2 years was associated with a decrease in serum homocysteine, which may contribute to the cardioprotective effect of HRT.

Improved cardiac function:

Recent studies have demonstrated menopause-related alteration in left ventricular wall thickness as well as Doppler indices of left ventricular filling. Furthermore, as estrogen receptors have been identified in the heart of primates and as both deprivation and replacement of sex hormones can alter left ventricular performance in female animals, direct myocardial effect of HRT cannot be excluded. From preliminary data, it appears possible that improved left ventricular filling can be added to the list of favourable effects of HRT.

Increase in prostacyclin production:

This action leads to direct vasodepressive effect that could favor improved cardiovascular function.

Promotion of calcium antagonist action:

Estrogen could mediate calcium antagonist action and promote vasodilatation.

Reduction in sympathetic innervation:

This is another mechanism by which cardioprotective effect could be mediated.

Decrease in atherosclerotic plaques:

Many of the above mentioned bio-effects of estrogen promotes decrease in atherosclerotic plaques.

Bone Economy and pharmacologic al estrogens:

Atleast 40 to 60 pg/ml of estradiol is necessary for bone protection. All estrogens effectively inhibit bone loss, provided an adequate dose is administerd. The optimum dose is 5 to 20 µg of ethinyl estradiol, 0.625 mg of conjugated estrogens or 1 to 2 mg of estradiol. Oral estrogen administration has been shown to inhibit long-term bone loss, and the average dose necessary has been 10 µg of ethinyl estradiol or 0.625 mg of Premarin.

Bone metabolism involves three biological functions, apart from the genetic factor: 1. osteogenesis which is effected by exercise and other physical activities; 2. calcification promoted by good diet and adequate calcium intake; and 3. prevention of decalcification (resorption), where estrogens play their pivot role. The bone mass is at its maximum near 30 years, and from 35 years there is a gradual decline in bone mass. With good physial activity/exercise and proper diet significant bone mass can be accumulated in the younger age. If maximum bone mass has been accrued in the younger age as reserve, the

bone loss will be balanced till the time of menopause and beyond. Otherwise the patient is exposed to the risk of osteopenia from the age of 35 years onwards.

Estrogens, by preventing bone resorption, supports bone mass if calcium supplementation is also maintained. Progestogens may have synergistic effect on bone density when added to estrogen because of their different modes of action and by their stimulating effect on bone formation. Combined therapy reports a net gain of 6.4% a year, and 12% increse in older population. Duphaston and desogestrel have been combined with ethinyl estradiol or premarin with maximal benefit.

Counseling and screening for estrogen therapy:
Estrogen administered in lowest possible dose for optimal indications is more beneficial and safe than being harmful. However, a prior medical and oncological screening and proper examination of genital organs and breast will be mandatory. The minimal tendency for cholylithogenesis should be kept in mind and such high risk subjects should be advised alternate measures.

Recruitment for hormone therapy should be optimized by a precise general, systemic and oncological evaluation. Admittedly, many healthy women of all age groups turn out to be suitable candidates for accepting hormone therapy. No doubt in such healthy women we can offer better quality of life and prevent various disease process by a recourse to low dose modern OC pill.

The subjects for cyclical hormones should have the following:

1. Complete medical and reproductive workup, before she is assigned for estrogen therapy.
2. Frequent surveillance at 6 months to one year interals is always appreciated.
3. routine sonographic study of pelvic organs could exclude pelvic pathology before starting hormones.
4. Cervical cytology or colposcopy will eliminate the risk of inadvertent use of hormones in women with cervical pathology.
5. Gynaecological disorders may be relative contraindication for hormonal contraception. However, certain gynaecological disorders such as small asymptomatic fibroids will not be a contraindiation. On the other hand the meaningful pelvic disease could be treated, and then estrogen-progestin therapy initiated. Cervical dysplasias can be treated effectively before these agents are prescribed.
6. Subtle medical disorders such as pre-clinical diabetes and mild hypertension under medical surveillance are not contraindications particularly when the modern micro-low dose OC combinations are considered.