PGH Menopause Clinic

A report from the Philippine General Hospital Menopause Clinic, prepared by the Section of Reproductive Endocrinology and Infertility of the Department of Obstetrics and Gynecology, UP College of Medicine
Overview of Menopause and Hormone Replacement Therapy

Hormone replacement therapy (HRT) for the Filipino menopausal women is not as widely accepted in the Philippines as compared to the western countries. Probably, the reason is that there are relatively fewer women openly complaining of menopausal symptoms. Many accept what they feel as just a part of the aging process. Very few realize that menopause is indeed an endocrinopathy, which can predispose them to serious medical disorders and that hormone replacement therapy can prevent these. Understanding the physiology and the physiologic changes during menopause will provide a good rationale for HRT in menopausal women.

To this end, the Philippine General Hospital Menopause Clinic was established to study the profile of the Filipino menopausal woman, to ascertain the efficacy and side effects of HRT and to determine the best HRT protocol suited for the Filipino menopausal patient. Armed with these, it is hoped that complete and holistic care can be afforded the Filipina at her climacterium. In this manual, the rationale, physiology, physiological changes of the menopause, as well as the desired and adverse effects of the various modes of therapy are discussed.

The Rationale of Hormone Replacement Therapy in the Menopause

The average life expectancy, even in developing countries is escalating. At the beginning of the 20th century, the average life expectancy is about 60 years but in the nineties, a newborn male can expect to live about 73 years, a newborn female about 80 years. In the Philippines, the figures are probably lower but certainly much higher than it was a century half a century ago. The average age of menopause in the Philippines is 48 years. After menopause, the Filipino woman can expect to live another 20-30 years as projected by Fleigers in his book “Road to Longevity.” (See Table).

A number of these women will have osteoporotic fractures, cardiovascular disease, depression, urinary disturbances and other minor complaints that can make the quality of life poorer. Prophylaxis with hormone replacement therapy (HRT) can prevent most of these complaints and may even lengthen a woman’s life. Even if all deaths from all forms of cancer were eliminated, life expectancy would increase by less than 2 years. If however, cardiovascular deaths are decreased, a significant improvement in life expectancy may be expected.

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Unfortunately, many lay persons and even medical personnel are not knowledgeable about the pathophysiology of the menopause. The patients who complain of distressing hot flushes, insomnia, dyspareunia, mood swings, depression etc. do not usually come for medical consultation and treatment. Because the Filipino culture usually provides continuous physical and emotional support for the elderly, the complaints among post-menopausal Filipino women may not be so prominent. Even if the signs and symptoms are minimal among these women, however, the metabolic and physical changes are probably the same as in the menopausal women worldwide.

The cost effectiveness of HRT will be realized if we can quantitate the reduction in the incidence of osteoporotic fractures, heart attacks, strokes and cancer. There will be fewer medical consultations among post-menopausal women. As these women have increasingly proven their worth as partners both in the home and in nation building, they will continue to be more productive.

Although menopause is a natural event, its consequences do not have to be accepted hook, line and sinker. There are technological advances in the management of the menopause as an endocrine deficiency state. With the...
improvement of its understanding, the impact of postmenopausal HRT on preventive medicine is steadily being recognized.

Physiology of the Menopause

Climacterium - physiologic period in life during which there is regression of ovarian function

<table>
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<th>Premenopause</th>
<th>Perimenopause</th>
<th>Postmenopause</th>
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<td>menstrua disturbances</td>
<td>= cessation of secondary to menses for at least 1 year due to decline in number of follicles</td>
<td>ovarian follicles</td>
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Concept of Menopause as an Endocrinopathy

> a specific endocrine gland has failed: the ovary
> specific endocrine products are deficient: estradiol-17β progesterone
> specific pathologic conditions develop because of endocrine deficiency: postmenopausal osteoporosis, urogenital atrophy, vasomotor instability, etc.
> treating the deficiency can prevent, delay or ameliorate many pathologic consequences of the endocrine deficiency: hormone replacement therapy (HRT)

Special Considerations on the Physiology of the Menopause

The median age of menopause in the Philippines is approximately 48 years. Although the average age of menarche today is earlier, menopausal age has not changed appreciably over the centuries. There is no relationship between the age of menarche and the age of menopause.

At 20 weeks of gestation the female fetus has the maximum number of oocytes. Oocyte depletion begins in utero, a process that continues until menopause. During the perimenopausal period, there are few remaining functional follicular units. As estrogen levels diminish, the endometrium is no longer stimulated. Bleeding becomes less regular and then eventually ceases.

The timing of this relative estrogen deficiency is probably genetically determined. A familial pattern in menopausal age suggests that there is a genetic predetermination.

Cigarette smoking is associated with early menopause. Smokers as a group have a median age of menopause that is approximately 1-2 years earlier than that of non-smokers. Pregnancy, lactation, and oral contraceptives all suppress ovulation, but they do not appear to change appreciably the age of menopause. Chemotherapy or radiation therapy can cause premature or earlier menopause. Some forms of premature ovarian failure do have a genetic basis and are more likely to occur if one’s mother had premature ovarian failure. There is no way one can predict the age at which a woman will enter the menopause.

Diagnosis of Menopause

Ovarian failure is best diagnosed by elevated levels of FSH. Serum E(2) level is not useful for the diagnosis of menopause. Low levels of E(2) can be found in the follicular phase, and normal E(2) levels maybe present in the perimenopausal period.

Physiologic Changes in the Climacterium

Respiratory Function

There is a decrease in both vital capacity and forced expiratory volume of the lungs as a woman ages. This, along with a decrease in chest wall compliance, impairs the cough reflex. The P02 however, is not significantly changed, and any increase in hypoxia should be considered abnormal.

Renal Function

Renal function declines progressively as a woman ages, with a consequent decline in creatinine clearance of about 1% per year. Since there is a decline in the absolute amount of creatinine due to decreased muscle mass, measurement of creatinine levels in serum should be used to estimate renal function. The renal plasma flow declines by about 10% per decade.

Carbohydrate Metabolism

Impaired glucose tolerance has been found in up to one-third of women over 60 years of age. The interpretation of increased glucose levels in women in higher age groups is more difficult because of decreased lean body mass, increased adipose tissue, impaired response to insulin, and a generally more sedentary life style.

Thyroid Function

The rate of iodine uptake falls by about 40% between the ages of 20-90. The production rate of thyroxine and the weight of the thyroid gland also decrease with age. Occult hypothyroidism is not uncommon and is best detected by a determination of the thyroid-stimulating hormone level in the serum.
Reproductive Tract Changes

In the absence of estrogen in the postmenopausal period, the resulting atrophic vaginal epithelium has an alkaline pH. There is a decreased number of lactobacilli and an increased susceptibility to symptomatic bacterial and trichomonal infection. Estrogen replacement can return the vaginal pH to normal levels between 3.75 to 4.0.

Consequences of Estrogen Deficiency

Acute : Menstrual changes
         : vasomotor phenomena
         : psychogenic manifestations
Intermediate : urogenital atrophy
Long Term : osteoporosis
         : cardiovascular changes

Menstrual Changes

• initiating event: decline in number of follicles
  → pituitary secretes more FSH
  → follicles mature irregularly
  → average estradiol decreases
    - failure of ovulation; no progesterone
    - endometrium fails to proliferate; atrophy
    - irregular menses → amenorrhea
  → later, LH rises as well
  → theca and adrenals continue to produce androgens
  → aromatization peripherally to estrone
    - obesity
    - anovulation; no progesterone
    - endometrial phyerplasia or CA

* all abnormal bleeding has to be investigated with endometrial biopsy or fractional curettage

Vasomotor Phenomena

• flash: a premonitory sensation that a flush is about to occur
• flush: a sensation of heat which begins in the torso or neck, spreading up to the neck and face or downward to the shoulders and chest (may be used interchangeably)
• proposed mechanism: declining systemic estrogen levels
  → abrupt downward shift of hypothalamic temperature set point
  → misperception that body is warmer than it should be
  → usual mechanisms to disperse heat activated
    - increase in skin conductance sweating
    - vasodilation
    - rise in skin temperature
  → decline in core temperature -à sweat evaporates
  → skin conductance returns to normal

Psychogenic Manifestations

Depression
Anxiety
Insomnia
Irritability
Loss of libido
Headaches
Difficulty in concentrating

• may be related to estrogen deficiency symptoms e.g. hot flushes
  → awaken at night
  → insomnia
  → lack of sleep
  → irritability
  → inefficiency at work
  → poor self-confidence
  → depression
  → loss of libido (also because of dyspareunia due to urogenital atrophy), etc. (“Domino Effect”)

• physiologic basis for symptoms should be ruled out first before dismissing them as part of menopausal syndrome
• psychological support for “change of life” is very important

Urogenital Atrophy

• possible mechanism of improvement of urogenital symptoms from HRT: estrogens act upon mucosa, submucosal vascular plexuses and connective tissue layer by increasing collagen content
• frequency, urgency and dysuria without bacteriuria = “urethral syndrome” - postmenopausally, may have different etiology from the condition diagnosed during the reproductive years often associated with sexual activity, but both respond to HRT

Osteoporosis

• definition: a condition in which reduction in bone mass per unit volume sufficiently compromises the skeleton, such that fractures may occur on minimal trivial trauma
• Risk Factors

A. Magnitude of peak bone mass
   - genetic:
     sex - female
     race - Caucasian, Oriental
     family history of osteoporosis
   - environmental:
     diet - low calcium, high protein
     exercise - lack of weight bearing exercise
     life style - sedentary
     abuse of drugs, alcohol, caffeine
B. Subsequent bone loss
- all of the above, plus
- early menopause or oophorectomy
- low body weight

Cardiovascular Changes
- at menopause, LDL cholesterol has age-related rate of increase; HDL remains relatively constant so ratio of HDL:LDL is decreased
- HDL2 fraction is the protective subfraction responsible for transporting cholesterol from peripheral tissues including arteries, to the liver for disposal; therefore, relatively lower levels links to atherosclerosis and coronary heart disease
- Estrogen has been proposed to prevent vasospasm and constriction in atherosclerotic coronary arteries thereby keeping the lumina dilated and preventing coronary events. At menopause, these changes are accelerated.
- Estrogens stimulate release of prostacyclins, which then inhibit thromboxane formation. Thromboxane causes thrombocytes to adhere to blood vessel walls where atheromatous plaques are formed. With estrogen deficiency the opposite may occur.

Menopause

| ↓ Estrogens — | ↓ prostacyclines — | ↑ thromboxane |
|↓ thrombocyte adhesion to blood vessel walls |

The Long Term Effect of Hormone Replacement Therapy

HRT in the Prevention of Osteoporosis

Two different types of osteoporosis have been described to explain the clinical heterogenicity of osteoporosis. Type I, or postmenopausal osteoporosis causes serious sequelae in women 15-20 years after the onset of menopause. Vertebral fractures, Colles fractures of the distal radius, and less commonly fractures of the proximal femur are the primary clinical features. Loss of dentition may also be observed. The trabecular skeleton (cancellous, spongy bone found in the vertebrae and flat bones) is selectively affected, and the rate of loss is three times normal. Cortical (compact) bone includes the long bones. The vertebrae are prone to acute collapse and loss of structural elements during the accelerated phase of demineralization at menopause. Estrogen deficiency, in turn leads to secondary increase in parathyroid hormone and increased secretion of calcitonin. There is an associated increased production of 1,25-dihydroxyvitamin D3, which results in impaired calcium absorption. Not all estrogen deficient women experience type I osteoporosis after menopause. There are other factors in addition to estrogen deficiency that contribute to bone loss. Type II, or senile osteoporosis affects women more commonly than men, by a 2:1 ratio. Hip and vertebral fractures are the primary clinical manifestations, but the proximal humerus, proximal tibia and pelvis are also affected. Vertebral fractures, typical of the multiple wedge type, produce dorsal kyphosis, or dowagers hump. This type of trabecular thinning is associated with a more gradual bone loss, which results in painless vertebral deformation. Type II osteoporosis is a senescent change affecting men and women alike. Type II osteoporosis is due to decreased osteoblast function (new bone formation) and decreased production of 1,25-dihydroxyvitamin D3, causing decreased calcium absorption leading to secondary hyperparathyroidism. This type of bone loss does not respond to estrogen therapy. These two processes of bone loss may occur concurrently in women over age 70 and contribute to osteoporotic morbidity.

Diagnosis of Osteoporosis

Several radiographic methods are available to assess bone density. Bone density can be assessed by lateral spine films, single- or dual-beam photon densitometry, or CT scan of the spine. The trabecular bones of the hips and spine are particularly important in clinical osteoporosis. Only dual-beam densitometry and CT scan are effective in evaluating the hip and spine, and only the CT scan can assess the trabecular bone. A CT scan provides the best correlation with bone biopsies and fracture rates. Decreased mineralization of the spine on CT scan is a strong indication of risk for osteoporosis.

Another new and efficient method for screening bone mineral density is the dual energy X-ray densitometry or (DEXA) which has been reported to be a quicker and more reliable method but experience with this is as yet limited. HRT has been show to be effective in preventing skeletal bone loss and has been reported to reduce the incidence of vertebral and hip fractures by about 50%. At menopause, there is a decrease in the cortical thickness of the metacarpals, radius, and spines. During the initial activation process of bone repair and renewal, there is activation of osteoblasts by parathyroid hormone or 1,25-dihydroxyvitamin D3, which leads to the secretion of intermediary proteins, which then stimulate osteoclasts to resorb bone. During the resorptive phase, local feedback from osteoclasts is relayed via cytokines to osteoblasts, which are then directed to lay down new bone. Osteoblasts possess receptors for estrogens. Estrogen deficiency leads to increased osteoclast activity and decreased osteoblast efficiency. Trabecular bone is lost more rapidly than cortical bone. This difference in bone loss is probably due to a much wider surface area for resorption in trabecular compared to cortical bone. Thus areas of the skeleton that have a high proportion of trabecular bone such as...
the spine, lose a larger percentage of bone secondary to estrogen deficiency. The increase in bone resorption at menopause is shown by increased urinary calcium and hydroxyproline excretion and elevated serum calcium and alkaline phosphatase values. Estrogen therapy to prevent bone loss after menopause is useful only if a woman is treated within 3 years of the menopause because the bone turnover is increased during the first 3 years after menopause. Doses of at least 0.625 mg of conjugated estrogen or 2 mg of oral estradiol per day are required to retain bone density. The lowest effective dose of conjugated estrogens is 0.625 mg, while micronized estradiol (1 mg) can retard bone loss of the radius. 0.625 mg of conjugated estrogens and 0.05 mg of estradiol administered by transdermal skin patch prevent bone loss in both the spine and hips, while the minimal effective dose of estrone sulfate that prevent loss of bone in the spine and hip are 0.625 mg and 1.25 mg, respectively.

All types of progestin compounds whether derived from C17, C19, or C21 slow the rate of cortical bone loss provided it is combined with estrogens.

There is also a demonstrable synergistic action of estrogen and calcium in preventing postmenopausal decrease in spine density. Calcium intake should be at least 800 mg/day. If the dose of conjugated estrogen is reduced to 0.3 mg per day, bone calcium will not be maintained. Conjugated estrogen administered in dosages of 0.3 mg per day with 1,500 mg of supplemental calcium is effective in maintaining bone calcium.

The use of calcitonin does not appear to affect significantly the development of osteoporosis. Salmon calcitonin is useful for the treatment of established osteoporosis.

Estrogens should be administered for at least 10-15 years after menopause in order to reduce the incidence of fracture, longer for women with low bone mineral density. The only way to identify a rapid bone loser is to measure spine density every 1-2 years. Biochemical markers of bone resorption such as fasting urinary calcium and hydroxyproline excretion found in rapid bone losers are not sensitive markers since there is a big overlap in normal values. The stabilizing effect of estrogen replacement therapy does not persist when estrogen treatment is discontinued. Since most bone loss occurs in the first 7-10 years following menopause, treatment is most effective if started early in menopause.

There are no definitive data suggesting that the fracture incidence is decreased with exercise. Bone mass, bone mineral content, and total body calcium maybe increased with vigorous exercise. Selective weight bearing exercise is recommended in association with estrogen therapy.

Sodium fluoride therapy has been tried in patients with established osteoporosis and is effective in increasing vertebral bone mass and preventing fractures. It is, however, associated with troublesome side effects, such as hematemesis, anemia, neuropathies and joint pain. A recently introduced slow release formulation may reduce some of the side effects.

A new drug, etidronate disodium (Didronel) was reported to increase bone density effectively by inhibiting osteoclast activity and subsequent bone resorption. It is useful in women with advanced osteoporosis and in those who cannot take estrogen.

Other measures than can reduce the risk of osteoporosis include eliminating smoking and avoiding excessive alcohol consumption. Studies have demonstrated diminished estrogen levels in smokers on estrogen replacement therapy and a twofold higher risk of vertebral fractures in smokers. Together with the evidence that menopause occurs earlier in smokers, this increased risk of osteoporosis is the most important evidence that smoking has an antiestrogenic effect.

The other factors that may contribute to osteoporosis are:
- Caucasian or Oriental race
- Family history
- short stature and small bones
- excessive leanness
- deficient dietary calcium intake
- sedentary life style
- nulliparity
- gastric or bowel resection
- protracted glucocorticoid therapy
- long-term use of anticonvulsants
- hyperparathyroidism
- thyrotoxicosis
- smoking
- alcohol abuse

Cardiovascular Disease and Hormone Replacement Therapy

Twice as many women die of cardiovascular disease (CVD) - related conditions than all gynecologic cancers combined. Numerous studies have documented the positive effect of HRT in the prevention of CVD.

Atherogenic CVD is a very complex multifactorial condition involving genetic predisposition, diet, smoking and physical activity. These are the factors that contribute to the development of atheromatous plaques in the vascular intima. This plaque serves as a nidus for subsequent clot formation and the development of
myocardial infarction or stroke. The injury to the arterial intima leads to platelet adhesion and release of intimal growth factor, defective utilization of low-density lipoprotein (LDL) cholesterol, lipid accumulation and increased glycosaminoglycan and collagen formation, proliferation of smooth-muscle cells and increased macrophage activity. Hyperlipidemia, disturbances in carbohydrate (CRHO) metabolism and hypertension are factors that may damage the endothelium.

The association between hyperlipidemia and CVD is a complex process. A 1% reduction in total serum cholesterol brings about a 2% subsequent reduction in heart attack rate. The normal for total serum cholesterol may vary from one race to another.

The exogenous and endogenous pathway of lipid-lipoprotein metabolism result in a net lipogenic effect. Dietary fats are absorbed as chylomicrons and catabolized by lipoprotein lipase, producing free fatty acids used as energy or stored in fat cells. Although chylomicrons are not atherogenic, their partially catalyzed remnants are very low density lipoproteins (VLDL) produced in the liver is hydrolyzed by lipoprotein lipase into intermediate density lipoprotein (IDL). Part of the IDL is transformed to LDL, the highly atherogenic fraction. LDL is atherogenic because these fractions are rich in cholesterol and triglycerides. LDL cholesterol transports about 2/3 of circulating cholesterol. Counterbalancing this is high density lipoproteins (HDL), synthesized in the liver and intestines, is converted to relatively cholesterol rich HDL2, which in turn is reconverted to cholesterol-poor HDL3 by hepatic lipase. The HDL subfractions, especially HDL2, are antiatherogenic and are involved in the transport of cholesterol from peripheral tissues to the liver and conversion to bio-acids. The protein components apolipoprotein A-I and apolipoprotein A-II serve as activator of the enzymes lecithin-cholesterol acyltransferase and hepatic lipase. High intracellular level of cholesterol suppresses the hepatic synthesis of LDL receptor thus elevating the LDL level through diminished uptake and metabolism and through conversion of VLDL to LDL. The imbalance among the atherogenic and antiatherogenic factors may produce vascular intimal damage.

Cholesterol, especially LDL increase in menopause. Estrogens enhance the catabolism of lipoprotein remnants, decrease LDL cholesterol levels, and increase levels of HDL especially HDL2 subfraction and its carrier protein apolipoprotein A-I and A-II. These changes produce an antiatherogenic effect manifested by a reduced incidence of strokes, cardiovascular deaths. HRT has been shown to result in a 41% reduction in mortality and 29% reduction in morbidity from acute myocardial infarction.

Progestogens are associated with increased levels of hepatic lipase activity resulting in increased hepatic supply of cholesterol, down-regulation of LDL receptors in the liver and elevated plasma LDL cholesterol levels. Progestins such as norethindrone, medroxy-progesterone acetate and norgestrel may abolish the estrogen’s beneficial effect on liprotein levels. Oral micronized progesterone is readily absorbed at a dose of 200-300 mg/day for 12 days and has very little effect on HDL cholesterol. A lower dose of 2.5 or 5 mg/day of medroxyprogesterone acetate in conjunction with conjugated estrogens does not negate the HDL elevating effect of estrogens. As a rule, post-menopausal women with intact uterus and who are at risk from CVD, should be treated with a high dose of conjugated estrogens (about 0.9 mg/day) and medroxyprogesterone at a dose of 8 mg per day for 14 days each month. The newer second generation non-androgenic gestogens (e.g. desogestrel, gestodene, norgestimate) or transdermally administered progesterone would be very useful in preventing endometrial hyperplasia or endometrial carcinoma during estrogen therapy. HRT does not increase the risk of atherogenesis.

Disturbances in Carbohydrate Metabolism

Persons with diabetes are at greater risk for CVD than persons without the disease. This can be due to several mechanisms such as CRHO-induced increase in VLDL, triglycerides and glycosaminoglycans, hyperinsulinaemia-induced proliferation of smooth-muscle cells, sorbitol-induced cellular changes and diabetes-induced changes in cells, platelets and lipid-lipoprotein moiety. Hyperglycemia and hyperinsulinemia leads to increased plasma levels of VLDL, triglycerides, decreased HDL cholesterol levels and hypertension probably resulting from resistance of peripheral tissue to insulin. Hyperinsulinism probably results from decreased peripheral insulin-receptor binding or a postreceptor defect that decreases insulin sensitivity in peripheral tissue. The hyperinsulinism increases levels of enzymes that control lipogenesis, thereby enhancing lipid synthesis in arterial wall and smooth-muscle cells.

Experiences with HRT have shown that progestogens may induce hyperinsulinism secondary to resistance of peripheral tissue to insulin and relatively minor degrees of hyperinsulinism and hyperglycemia may predispose persons to atherogenic disease.

Estrogens do not materially affect carbohydrate metabolism and are safe to give to postmenopausal women with diabetes as long as close monitoring is done.

Hypertension

The shearing hemodynamic force in hypertension may initiate intimal damage. Oral estrogens increases
Coronary artery disease is increased from 2-10 fold when prescribed with estrogen do not adversely affect cardiovascular disease.

Women who develop urinary stress incontinence in their post menopausal years are treated with estrogen. In estrogen-deficient women this form of hormonal therapy causes a proliferation and thickening of the urethral mucosa, increased intraabdominal pressure transmission to the urethra, and improved contraction of the periurethral muscle. Estrogen receptors have been identified in the urethra. The changes produced by estrogen therapy may result in improvement or cure of stress urinary incontinence in post menopausal women. Postmenopausal women treated with oral estrogen replacement report subjective improvement in symptomatology of frequency, urgency, and stress urinary incontinence. Although estrogen does not increase urethral pressure or functional length, the pressure transmission ratio can be improved markedly. The effect of estrogen is to increase the efficiency of the urethral closure mechanism. However, this is of no value in the treatment of genuine stress urinary incontinence that occurs in women in their reproductive years. The route of estrogen administration is not crucial, as the vaginal mucosa is one of the tissues that is most sensitive to estrogen.

Blood Clot Formation

Most of the coagulation factors in the plasma are increased by the oral use of sex steroids. This is the result of the hepatic first-pass metabolism of these drugs and their effect on the synthesis of vitamin K procoagulant factors. Only 25% of factor VIII is required for hemostasis although the normal range could be from 60-200%. Thus even significant changes in plasma levels of coagulation have very little clinical significance. There are no tests that can measure hypercoagulable state, with the possible exception of fibrinogen and protein C studies. Oral estrogen increases the various coagulation factors but also increases blood flow, which will not favor clot formation.

Progesterone may decrease blood flow but have little effect on coagulation factors per se. Studies in surgically or naturally menopausal women, showed a shift away from clot formation toward clot inhibition and fibrinolysis as evidenced by increases in antithrombin III antigen, alpha2-antitrypsin antigen, and plasminogen activity. Plasminogen activity can be increased by about 10-32% in postmenopausal women given estrogen and progestin HRT. Progestins increase plasminogen activity to level that can prevent thrombosis. This is probably the reason why venous and arterial thromboses occur very infrequently in postmenopausal women taking estrogen-progestin HRT. Thrombosis in the arteries occurs only after platelet activation. Platelet activation involves prostacyclin and thromboxane A2. Prostacyclin is produced by the vascular intima and induces vasodilatation and decreased platelet aggregation. Thromboxane A2 causes vasoconstriction and platelet adhesion. Progesterone seems to have a protective effect because prostacyclin production is either unchanged or increased. The current concept is that progestogens when prescribed with estrogen do not adversely affect cardiovascular disease.

Coronary artery disease is increased from 2-10 fold in smokers. Smoking has been found to be a greater risk factor than hypertension, hypercholesterolemia, or glucose intolerance. Smoking may produce this effect by the influence of nicotine on the sympathetic nervous system, the desaturation of hemoglobin by carbon monoxide, and an increase in platelet adhesiveness. Cigarette smoking is not a contraindication for ERT.

Other Benefits of HRT

Other Benefits of Estrogen Replacement Therapy

Women who develop urinary stress incontinence in their post menopausal years are treated with estrogen. In estrogen-deficient women this form of hormonal therapy causes a proliferation and thickening of the urethral mucosa, increased intraabdominal pressure transmission to the urethra, and improved contraction of the periurethral muscle. Estrogen receptors have been identified in the urethra. The changes produced by estrogen therapy may result in improvement or cure of stress urinary incontinence in post menopausal women. Postmenopausal women treated with oral estrogen replacement report subjective improvement in symptomatology of frequency, urgency, and stress urinary incontinence. Although estrogen does not increase urethral pressure or functional length, the pressure transmission ratio can be improved markedly. The effect of estrogen is to increase the efficiency of the urethral closure mechanism. However, this is of no value in the treatment of genuine stress urinary incontinence that occurs in women in their reproductive years. The route of estrogen administration is not crucial, as the vaginal mucosa is one of the tissues that is most sensitive to estrogen.

Even women with procidentia uteri who are candidates for hysterectomy will benefit from a course of estrogen therapy prior to surgery to improve tissue tone. Sexual dysfunction following hysterectomy can be improved with estrogen replacement. Hormone replacement following oophorectomy should be considered. There is a loss of energy and sense of well-being after oophorectomy. Estrogen-androgen therapy administered to women after bilateral oophorectomy will improve energy level and sense of well-being. This is not observed in women who had undergone natural menopause and who had not had bilateral oophorectomy. The post operative use of estrogen has not been demonstrated to improve the loss of libido after hysterectomy, nor does it appear to improve the ability to reach orgasm. Estrogen, however, is effective against dyspareunia. Orgasm is less likely to be affected when a supracervical hysterectomy is performed.
turing ovarian failure or hypogonadism due to hypothalamic-pituitary suppression, such as that occurring in exercise induced amenorrhea and anorexia nervosa.

HRT has shown improvement of both cognitive and affective end points with estrogen use in areas including memory, insomnia, anxiety and irritability.

With aging, noticeable changes in the skin occur. A generalized thinning is accompanied by a loss of elasticity which results in wrinkling. Decrease in skin thickness and collagen content have been identified in the skin of the thighs and forearms of women after menopause. HRT has been shown to increased both the thickness and the collagen content of the skin with the greatest effects seen in women with low values before therapy.

Hormone Replacement Therapy

Routes of Administration

The dermal patches available are:

- Estraderm TTS (Estradiol)

The oral sequential preparations are:

1. Prem-Pak (10 tab each containing natural conjugated estrogen (Premarin) 62 μg.
   - Colprone - 5 mg. 21 tab each containing natural conjugated estrogen (Premarin) 625 μg.
2. Trisequens (10 mg white tab each containing Norethisterone acetate 1 mg, Oestradiol 2 mg, 2 blue tab each containing oestradiol 2 mg, 6 red tab each containing oestradiol 1 mg.
3. Climen (10 tab each containing Cyproteron acetate 1 mg, estradiol valerate 2 mg, 11 tab each containing estradiol valerate 2 mg.

The continuous combined:

1. Prempro or Premel (Conjugated estrogen 0.625 mg and Medroxy progesterone 2.5 mg.)
2. Kliogest (Norethisterone acetate 1 mg, Oestradiol 2 mg)

The pure estrogen preparations are:

1. Premarin (Natural conjugated estrogen)
2. Progynova (Estradiol valerate)
3. Estrofem (Estradiol)

The newest in the market is Raloxifen, a selective estrogen receptor modulator (Serm)-Evista, 60 mg tab.

Special Considerations on the Pharmacokinetics and Pharmacodynamics of Hormone Replacement Therapy

Mode of Administration of Estrogen

Oral administration of estradiol leads to a rise in circulating estrone levels because of conversion in the gastrointestinal tract. There is no evidence that estrone, a weak estrogen, is not a suitable form of estrogen replacement. Oral administration of estradiol causes high concentrations of drugs to pass through the liver after absorption. This leads to elevation in a number of hepatic products that can have either beneficial or detrimental effects. Oral estrogens induce marked, dose-dependent changes in serum lipids; reduction in total and low density lipoproteins (LDL)-cholesterol, and increase in high-density (HDL) cholesterol. However, oral estrogens also increase serum triglycerides, which constitute a significant risk factor for cardiovascular disease in women aged 50 and above.

Percutaneous administration of estrogen in the form of transdermal patches demonstrate absorption of unaltered estradiol leading to physiologic levels of estradiol in the serum. Transdermal estradiol reduces LDL cholesterol. HDL- cholesterol is less consistently altered, though the HDL(2)/(HDL(3) ratio appears to be influenced beneficially. Preliminary studies have shown that transdermal estradiol impairs formation of lysolecithin so inhibiting formation of chemically modified LDL particles, which are considered atherogenic. Transdermal estradiol alters the composition of lecithin, whose fatty acids are prime precursors of prostacyclin and thromboxane A2 which may reduce the risk of thrombosis formation. Transdermal estradiol efficiently reduces hot flashes to the same extent as oral preparations.

Transdermally administered estrogens do not pass through the liver in high concentrations, thereby losing the beneficial effect of elevating high density lipoproteins. It is not known whether high concentrations of estrogen in the liver is necessary to increase calcium absorption and resorption from bowel and kidney through vitamin D metabolism. A recent study demonstrated that over a period of 2 years, administration of 3 mg of estradiol cream daily resulted in bone mineral conservation. This cream produced much higher circulating levels of estradiol than are noted with the patches.

Vaginal administration of estrogen cream will give relief of vaginal symptoms. It is absorbed systemically but absorption is erratic. Vaginal administration of estrogen has not been demonstrated to reduce the risk of cardiovascular disease. Vaginal cream is effective for relieving the symptoms of vaginal atrophy, and at high doses (2-4 gm) of conjugated estrogen cream daily can lead to some systemic absorption. At low doses (1 mg daily or less) the cream can convert the vaginal smear to a pattern similar to that found in premenopausal women, but will have little systemic effect. Micronized estradiol tablets, placed in the vagina, are readily absorbed into the circulation. If estrogens are given vaginally, the use of progestin challenge as a bio-assay of the endometrial
proliferation should be performed. If administration of progestin as a challenge does not result in vaginal bleeding, then the patient is at low risk and the challenge should be repeated at periodic intervals. If bleeding occurs in response to the progestin challenge, then the estrogen administration should be combined with a continuous or periodic progestin administration.

The other forms of estrogen administration is by estradiol- polymeric silicone (Silastic) capsules inserted subcutaneously or by gels applied to the skin.

**Dosage Regimens**

- Continuous unopposed estrogens: major hazard is endometrial hyperplasia/CA in women with intact uteri
- Cyclic estrogen with sequential progestogen (0.625 mg conjugated estrogens on Days 1-25 of month, combined with 5 mg to 10 mg of medroxyprogesterone acetate or 10 to 20 mg of dydrogesterone or 5 mg of Medrogestone on Days 13-25) - withdrawal bleeding may be bothersome; symptoms may recur during hormone free period
- Continuous estrogen with sequential intermittent progestosterone
  - (0.625 mg conjugated estrogens everyday plus 5 or 10 mg medroxyprogesterone acetate or a suitable progestogen on calendar days 1-13 or 14 every month) - may still have withdrawal bleeding but symptoms do not recur because there is no estrogen-free period
- Continuous estrogen with low dose progestosterone (0.625 mg conjugated estrogens plus 2.5 mg medroxyprogesterone acetate or 0.5 or 1 mg norethindrone everyday) - amenorrhea is achieved after a shorter period of time
- Transdermal estrogen patch (0.025 or 0.05 mg/day Estraderm changed every 3.5 days - very convenient for women without uteri but does not make use of the cardiovascular advantage of first pass effect of oral estrogens which alters HDL:LDL ratio; has the advantage of not inducing changes in liver enzymes which may increase coagulation factors or renin substrate
- Special considerations on the pharmacokinetics and pharmacodynamics of hormone replacement therapy

**Adverse Effects with HRT**

The risks of HRT include endometrial cancer, venous thrombosis, hypertension and cholelithiasis. Side effects include headache, nausea, vomiting abdominal distention or bloating, edema, breast tenderness, enlargement of uterine leiomyomas, chloasma and vaginal bleeding. The estrogen induced fluid retention may aggravate certain conditions such as epilepsy, asthma, migraine, heart and kidney disease. The progestins in HRT may give rise to side effects such as breast tenderness, urticaria, pruritus, acne, alopecia, hirsutism, vaginal bleeding, edema, change in weight, cholestatic jaundice, anaphylaxis, depression, pyrexia, insomnia, nausea, dysmenorrhea and somnolence.

Women given daily continuous estrogen with supplemental progestin therapy for the first 10-14 days of each cycle will experience withdrawal bleeding. The bleeding usually occurs 2 days after completion of the progestin therapy and lasts for 3-4 days. If the bleeding began prior to day 10 of progestin therapy it was likely to arise from proliferative endometrium but if the bleeding began after day 10 of therapy, it was associated with full secretory transformation. Women in the former group remain at high risk for endometrial hyperplasia and potentially endometrial adenocarcinoma, but those who had bleeding after day 10 experienced the full therapeutic benefit of progestin therapy and no further modification of regimen was indicated. Increasing the duration of progestin exposure appears to be more important than increasing the dose of progestin to protect the endometrium. The dose of 10 mg of medroxyprogesterone acetate is known to be effective in preventing endometrial hyperplasia and the incidence of endometrial hyperplasia in inversely related to the duration of progestin exposure. Maximal protective effects are achieved when progestin therapy is given for 12-13 days. Once secretory changes are induced, there does not appear to be any benefit in offering a more protracted course of progestin therapy.
Increasing estrogen dose induces more intense endometrial proliferation and is associated with a higher risk of endometrial hyperplasia unless progestin is given. Symptoms associated with the progestin component may resolve when the daily dose of medroxyprogesterone is reduced from 10 mg to 5 mg. The lower cyclic dose does not offer quite as much protection as the higher one. Withdrawal bleeding can be eliminated by reducing the conjugated estrogen from 0.625 mg to 0.3 mg or by adding 2.5 mg of medroxyprogesterone daily.

Estrogen-only therapy can be given, but endometrial biopsy should be performed prior to the initiation of therapy and annually thereafter. Endometrial hyperplasia requires either discontinuation of estrogen therapy or addition of a progestational agent. Transvaginal ultrasound endometrial measurements are useful in detecting the possibility of excessive endometrial proliferation when the endometrial thickness exceeds 6 mm.

Contraindications to Hormone Replacement Therapy

Absolute:
- presence of hormone dependent neoplasms such as breast and endometrial cancer
- active or recent thromboembolic disease

Relative:
- hepatic insufficiency
- cholecystolithiasis
- renal dysfunction
- impaired glucose tolerance or diabetes mellitus
- uncontrolled hypertension
- heart failure
- fibrocystic disease of the breast
- uterine leiomyoma

Drug Interactions
- impaired activity of estrogens may be seen when given with preparations which induce microsomal liver enzymes e.g. barbiturates, hydantoins, carbamazepine, meprobamate, phenylbutazone or rifampicin

Contraindications to HRT include unexplained vaginal bleeding, acute liver disease, chronically impaired liver function, recent vascular thrombosis, breast and endometrial carcinoma. Seizure disorders, hypertension, uterine leiomyomas, familial hyperlipemia, migraine, thrombophlebitis, endometriosis and gallbladder disease require close monitoring. If HRT is contraindicated, other medication can be used to help women with vasomotor symptoms. Medroxyprogestosterone acetate (10-40 mg daily), Megestrol acetate (20-80 mg daily), and clonidine (0.2-0.4 mg daily) can reduce the occurrence of hot flushes.

Breast cancer has been associated with circumstances that promote long, uninterrupted exposure to estrogen. Early menarche and late menopause are associated with increased risk of breast cancer. Bilateral oophorectomy without ERT reduces the risk of subsequent breast cancer by 40-70%, and this is more emphasized in women who lose ovarian function before the age of 35. Untreated women with gonadal dysgenesis do not develop breast cancer. Although there are evidences that there is an increased risk for breast cancer with protracted endogenous estrogen exposure, there is no clear evidence confirming the increased risk as a consequence of exogenous estrogen exposure. There is no evidence that progestin therapy reduces the risk of developing breast cancer.
Drugs Mentioned in the Treatment Guideline

The following index lists therapeutic classifications as recommended by the treatment guideline. For the prescriber's reference, available drugs are listed under each therapeutic class.

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