REVIEW OF LITERATURE
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LIPIDS AND LIPOPROTIENS -

Cholesterol:

Cholesterol is an amphipathic lipid and as such is an essential structural component of membranes and of the outer layer of plasma lipoproteins. Lipoprotein transport free cholesterol in the circulation where it readily equilibrates with cholesterol in other lipoproteins and in membranes.

It is synthesized in many tissues from acetyl-CoA and is ultimately eliminated from the body in the bile as cholesterol or bile salts. Cholesterol is the precursor of corticosteroids, sex hormones, bile acids and vitamin D.

It occurs in foods of animal origin such as egg yolk meat, liver and brain and a major risk factor for atherosclerosis (Harper 1996).
**Triglyceride:**

Triglyceride is synthesized from phosphatidate which in turn is synthesized from acylation of glycerol 3 phosphate by enzyme glycerol 3 phosphate acyl transferase. These are the major energy storing lipids (Harper 1996). Some studies have shown that plasma triglycerides levels >130-150mg/dl are associated with low HDL cholesterol and small dense LDL particles. Meta analysis of several prospective population studies confirms that triglyceride concentrations are independent risk predictor of coronary heart disease.

**Lipoproteins:**

Lipoproteins are spherical particles made up of hundreds of lipid and protein molecules. The major lipids of the lipoproteins are cholesterol, triglycerides and phospholipids. Triglycerides and cholesterol esters (esterified form of cholesterol)
are hydrophobic and forms the core of the lipoprotein.

Phospholipids and a small quantity free (unesterified) cholesterol are amphipathic and cover the surface of the particle. According to the density lipoproteins of plasma have been grouped into four groups. As the proportion of lipid to protein in a lipoprotein increases, the density decreases. According to increase of density they are classified as follows:

**Compositions of the lipoproteins in plasma**

<table>
<thead>
<tr>
<th>Fraction</th>
<th>Source</th>
<th>Density</th>
<th>Composition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Protein (%)</td>
</tr>
<tr>
<td>Chylomicrons</td>
<td>Intestine</td>
<td>&lt;0.95</td>
<td>1-2</td>
</tr>
<tr>
<td>VLDL</td>
<td>Liver (Intestine)</td>
<td>0.95-1.006</td>
<td>7-10</td>
</tr>
<tr>
<td>LDL</td>
<td>VLDL</td>
<td>1.006-1.019</td>
<td>119</td>
</tr>
<tr>
<td>LDL</td>
<td>VLDL</td>
<td>1.019-1.063</td>
<td>21</td>
</tr>
<tr>
<td>HDL</td>
<td>Liver &amp; Intestine</td>
<td>1.063-1.125</td>
<td>33</td>
</tr>
<tr>
<td>HDL</td>
<td>VLDL, Chylomirons</td>
<td>1.125-1.210</td>
<td>57</td>
</tr>
<tr>
<td>Albumin</td>
<td>Adipose tissue</td>
<td>&gt;1.281</td>
<td>99</td>
</tr>
</tbody>
</table>

VLDL - Very low density lipoprotein,  LDL - Low density lipoprotein  
IDL - Intermediate density lipoprotein,  HDL - High density lipoprotein

**Apolipoproteins:**

The protein moiety of a lipoprotein is know as an apolipoprotein. The apolipoproteins (apos) provide structural stability to the lipoproteins and determine the metabolic fate of the particles upon which they reside.
## Apolipoproteins of Human Plasma Lipoproteins

<table>
<thead>
<tr>
<th>Apolipoprotein</th>
<th>Lipoprotein</th>
<th>Metabolic Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apo AI</td>
<td>HDL, Chylomicrons</td>
<td>Structural component of HDL, LCAT activator</td>
</tr>
<tr>
<td>Apo Al</td>
<td>HDL, Chylomicrons</td>
<td>Unknown</td>
</tr>
<tr>
<td>Apo IV</td>
<td>HDL, Chylomicrons</td>
<td>Unknown, possibly facilitates transfer of other apos between HDL and Chylomicrons</td>
</tr>
<tr>
<td>Apo B48</td>
<td>Chylomicrons</td>
<td>Necessary for assembly an secretion of chylomicrones from the small intestine</td>
</tr>
<tr>
<td>Apo B100</td>
<td>Chylomicrons, VLDL, IDL, LDL</td>
<td>Necessary for secretion of VLDL from liver, ligand for LDL receptor</td>
</tr>
<tr>
<td>Apo CI</td>
<td>Chylomicrons, VLDL, IDL, HDL</td>
<td>May inhibit hepatic uptake of chylomicron and VLDL remnants</td>
</tr>
<tr>
<td>Apo CII</td>
<td>Chylomicrons, VLDL, IDL, HDL</td>
<td>Activator – lipoprotein Lipase</td>
</tr>
<tr>
<td>Apo CIII</td>
<td>Chylomicrons, VLDL, IDL, HDL</td>
<td>Inhibitor of lipoprotein Lipase, may inhibit hepatic uptake of chylomicron and VLDL remnants</td>
</tr>
<tr>
<td>Apo E</td>
<td>Chylomicrons, VLDL, IDL, HDL</td>
<td>Ligand for finding lipoprotein to LDL receptor.</td>
</tr>
</tbody>
</table>

LCAT: Lecithin cholesterol acyl transferase.
LDL-

Estrogen replacement therapy/HRT has been demonstrated to have a beneficial effect on several modifiable risk factors for CHD, including unfavorable lipid profiles. Elevated blood lipid levels are particularly important risk factors for the development of CHD in women. The Framingham Study demonstrated that total cholesterol levels increased after menopause in a cohort of 2873 women followed up since 1948. This increase was primarily due to an increase in low-density lipoprotein (LDL) cholesterol levels. There was also a slight decrease in high-density lipoprotein (HDL) cholesterol levels after menopause. Similar changes were reported in a cross-sectional study of 542 healthy, nonobese women 18 to 70 years of age. These alterations in blood lipid levels likely contribute to the increased risk of CHD in postmenopausal women. A recent meta-analysis of 8 trials of 3-hydroxy-3-methylglutaryl coenzyme A
(HMG-CoA) reductase inhibitors concluded that reduction in the risk of mortality from CHD is proportional to the net reduction in total cholesterol levels. The cardioprotective effect of ERT/HRT in observational studies appears to be partly due to its ability to alter favorably the blood lipid profile. Several clinical studies have shown that ERT/HRT reduces plasma LDL levels.

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, 875 healthy, postmenopausal women were studied using a randomized, double-blind protocol. The group receiving oral conjugated equine estrogen (CEE) (0.625 mg/d) had a 10% to 12% reduction in LDL levels during the 3 years of treatment. The addition of medroxyprogesterone acetate (MPA) or micronized progesterone to CEE did not affect this decrease in LDL levels.

In a randomized, double-blind study designed to investigate the influence of estrogen dose on plasma
lipids, 31 postmenopausal women were administered 2 dosages of CEE, 0.625 mg/d or 1.25 mg/d. Low-density lipoprotein cholesterol levels were reduced by 15% and 19%, respectively.

Differences between oral estrogen treatments in reducing LDL levels have been reported in some but not all studies. McManus and coworkers demonstrated a 13.8% (P<.01) decrease in LDL levels in postmenopausal women treated with CEE (0.625 mg/d), compared with 7.8% (P<.05) with estradiol valerate (1 mg) and 12.7% (P<.05) with estradiol (2 mg) and MPA (1 mg). No significant effect was seen with either estradiol (2 mg) and norethidrone (1 mg) or transdermal estradiol (50 μg). All doses were given once daily for 4 weeks.

In a study among healthy, nonsmoking, postmenopausal women, LDL levels decreased by 15% (P<.001) in women treated with CEE (0.625 mg/d) for 3 months, compared with 14% (P<.005) with oral estradiol (2 mg/d). No effect was
seen with transdermal estradiol (0.1 mg twice a week). In a more recent study, Egarter et al compared the effects of estradiol valerate (2 mg) and MPA (10 mg) with 0.625-mg CEE and 10-mg medrogestone and reported a significant decrease in LDL levels with estradiol valerate and MPA (P<.01) after 6 months but not with CEE. Because the doses of estradiol valerate and CEE used in the study are thought to produce an equal level of estrogenic activity, the difference in LDL reduction is likely the result of the dose and/or hormonal properties of the progestin components. Variations in the percentage of LDL reduction with ERT/HRT between studies are often because of the differences in baseline levels of LDL.

**HDL-**

Beneficial reductions in LDL levels with the use of ERT/HRT are often accompanied by beneficial increases in the level of HDL. High-density lipoprotein facilitates the removal of cholesterol
from extrahepatic tissues, and its levels are inversely associated with the risk of CHD, especially in women.

In the PEPI trial, postmenopausal women assigned to treatment with unopposed CEE (0.625 mg/d) exhibited a 10% to 12% increase in HDL levels during the first 12 months of the study. The HDL level gradually decreased during the next 2 years but remained 7% above baseline at the conclusion of the study. The addition of MPA to CEE diminished but did not negate the beneficial alteration of HDL with HRT in the PEPI trial. In contrast, micronized progesterone did not significantly attenuate the HDL benefit associated with CEE. Thus, the magnitude of the decreased benefit may depend on the type, dose, and dosing regimen of the progestin used.

Studies that have examined treatment with other oral estrogens in addition to CEE have generally found similar increases in HDL levels. In a
3-month study by Walsh et al, CEE, 0.625 or 1.25 mg/d, increased HDL levels by 16% to 18%, while oral micronized estradiol, 2 mg/d, increased HDL levels by 15%; the increase in the HDL level was because of an increase in the HDL2 fraction. Transdermal estradiol (0.1 mg twice a week) had no effect.

Twenty-two healthy, hysterectomized, postmenopausal women who were treated with oral estradiol valerate (1 mg/d), CEE (0.625 mg/d), or transdermal estradiol (50 µg/d) for 4 weeks in a crossover design study had a 7.1% increase in HDL levels with estradiol valerate (P<.01) and a 6.3% increase with CEE (P<.05) at the end of treatment but no significant change (P>.05) with transdermal estradiol. In a substudy conducted by these authors and reported in the same article, among 18 healthy,

Nonhysterectomized, postmenopausal women, estradiol (2 mg/d) combined with norethisterone (1 mg/d) significantly lowered HDL
levels after 4 weeks. When estradiol was combined with MPA (5 mg/d), it produced a nonsignificant decrease (P > .05) in HDL levels. The reduced effect on HDL levels of transdermal estradiol is because of its minimal effect on hepatic metabolism since it bypasses the portal circulation, although Pownel reported that CEE and transdermal estradiol had equally positive effects on total cholesterol and HDL levels.

TRIGLYCERIDE-

Several studies have shown that the use of ERT/HRT results in an increase in triglyceride (TG) levels, which may also be associated with CHD risk and mortality. For example, Austin et al analyzed population-based prospective studies, 5 of them involving women, and found a statistically significant increase in the risk of incident CVD of 14% in men and 37% in women, when adjusted for HDL-C level and other risk factors.
Bass et al followed up 1405 postmenopausal women for an average of 14 years and reported a strong correlation between TG levels and death due to CVD. Triglyceride levels greater than 4.50 mmol/L (398 mg/dL) were associated with a more than 3-fold increase in the risk of CVD mortality. Manolio et al also found a significant association (P<.05) of TG levels with risk of CHD in 5 of 6 cohort studies of middle-aged women younger than 65 years; however, the studies' statistical power was not adequate to determine whether the TG level was an independent risk factor.

In a randomized, double-blind, crossover study, Walsh et al reported 24% and 38% increases in total TG levels in women receiving 0.625-mg/d and 1.25-mg/d CEE, respectively, for 3 months. Oral estradiol (2 mg/d) increased total TG levels by 24%, but transdermal estradiol was without effect.

Similar increases following the administration of CEE (0.625 mg/d) were reported in
the PEPI trial as well as in clinical trials by Lobo et al and Miller et al.

The addition of progestins to CEE does not appear to influence the TG response. However, in a retrospective subset analysis by the Menopause Study Group, postmenopausal women with baseline TG values greater than 1.808 mmol/L (160 mg/dL) reduced their TG levels by 13.7% following the continuous or cyclic administration of CEE plus MPA. Although it has been suggested that the increase in TG levels with HRT use is unlikely to be detrimental for patients without existing hypertriglyceridemia, the clinical relevance has not been fully established.

**APOLIPOPROTEIN A₁ & B-**

The apolipoproteins (apos) provide structural stability to the lipoproteins and determine the metabolic fate of the particles upon which they reside. They were named in an arbitrary alphabetical
order and, for the purposes of this discussion, will be described in relation to their association with lipoprotein classes.

Apo AI, apo AII, and apo AIV are found primarily on HDL. There are two forms of apo B—apo B100 and apo B48. Apo B100 is the major apolipoprotein of VLDL, IDL, and LDL, comprising approximately 30, 60, and 95% of the protein in these lipoproteins, respectively. Plasma levels of HDL cholesterol and apo AI are inversely related to risk for CHD.

**LIPOPROTEIN (a)-**

Apoprotein(a), a large glycoprotein that shares a high degree of sequence homology with plasminogen, is made by hepatocytes and is secreted into plasma where it forms a covalent linkage with the apo B100 of LDL to form lipoprotein(a). The physiologic role of lipoprotein(a) is not known, but elevated levels
are associated with an increased risk for atherosclerosis.

Lipoprotein(a) is a unique molecule comprising a lipoprotein particle resembling LDL cholesterol that is covalently bonded to apo(a), a large plasma glycoprotein. The individual characteristics of these 2 components are thought to be responsible for the apparent pathogenic role of Lp(a), which has no known physiologic function. The LDL cholesterol component likely contributes to atherogenesis, whereas apo(a), similar in structure to plasminogen, may promote thrombosis. Thus Lp(a), which has been isolated in the arterial wall at sites of atherosclerosis, may serve as a link between the pathogenic processes of atherosclerosis and thrombosis.

A beneficial effect of ERT/HRT is the reduction of lipoprotein(a) [Lp(a)]. Lipoprotein(a) is a complex of an LDL-like particle and apolipoprotein A (apoA). Elevations in Lp(a) have been associated
with CHD and thrombotic stroke. The mechanism of this relationship is not known, but it is thought that because apoA and plasminogen are homologous, elevated levels of Lp(a) may interfere with fibrinolysis and therefore promote thrombosis. Estrogen replacement therapy/HRT appears to favorably alter Lp(a) levels.

In a randomized, double-blind, crossover study of 100 women who had undergone hysterectomies, 6 months of oral estradiol (2 mg/d) reduced Lp(a) levels by nearly 10%. After 12 months, no further decrease was reported.

Shewmon et al reported a 24% decrease in Lp(a) levels in postmenopausal women receiving CEE (0.625 mg/d) for 2 months, and Lobo et al\textsuperscript{26} reported a 32% decrease in Lp(a) levels after 6 months of treatment with CEE (0.625 mg/d) in women who had surgical menopause. In contrast, transdermal estradiol (50 μg/24 hours, twice a week) reduced Lp(a) levels by approximately 10%. Data
from the PEPI trial indicated that progestins added to CEE did not alter the beneficial changes in Lp(a) levels. Mosca et al\textsuperscript{30} also showed a significant (16%; $P = .02$) reduction in Lp(a) levels with combination HRT; however, only a small percentage of women showed a reduction below a critical threshold level of less than 30 mg/dL.

**ESTROGENS-**

**Nonsynthetic (natural) estrogens:** Nonsynthetic estrogens may be given orally, vaginally, transdermally, or subcutaneously. In general, conjugated estrogens are twice as potent as estrone preparations (e.g., estropipate) because they also contain equine estrogens, which are very potent. In particular, they have a long half-life, in part as a result of their storage in and slow release from adipose tissue.

Conjugated estrogens given orally at 0.3 or 0.625 mg, estropipate 0.625 or 1.25 mg, or micronized
or 1 mg is most commonly prescribed. These doses maintain the mean peak serum estradiol level at about 30 to 40 pg/mL (110 to 150 pmol/L), similar to that during the early follicular phase of the menstrual cycle, and the estrone level at 150 to 250 pg/mL (555 to 925 pmol/L). These doses are generally effective in relieving menopausal symptoms and preventing osteoporosis. The lowest dose may be used for women who experience adverse effects. However, whether lower doses confer maximal therapeutic benefit is unknown.

Enterohepatic circulation contributes to the prolonged effect of oral estrogens. Thus, patients with altered gut flora (eg, due to antibiotic use) may not sufficiently hydrolyze these conjugates, thereby preventing reabsorption, and may need higher doses. Also, patients given long-term phenytoin have enhanced glucuronidation and therefore excrete
estrogens more rapidly; they too may need higher doses.

Because the concentration of oral estrogen is 4 to 5 times higher in the portal than in the general circulation, more estrogen is presented to hepatocytes than to cells of other organs. Thus, the liver is more affected by estrogens given orally than by those given parenterally. Although many of these effects on the liver may be deleterious (eg, stimulating renin-substrate and coagulation factors), some effects may be beneficial (eg, increasing high-density lipoprotein [HDL] cholesterol levels, decreasing low-density lipoprotein [LDL] cholesterol levels).

Vaginally applied estrogens are absorbed and enter the systemic circulation, achieving about one fourth the circulatory level of an equal oral dose. Specifically, vaginal estrogens exert a potent local effect; 0.3 mg of conjugated estrogens given vaginally produces the same degree of epithelial
maturation as does 1.25 mg po. Continued use of vaginal estrogen increases blood estrogen levels because of enhanced transfer across a healthier, better vascularized epithelium.

Silastic rings containing estradiol may be placed in the vagina and changed every 3 months; these rings introduce negligible quantities of estradiol into the systemic circulation.

Transdermal estradiol patches 50 μg/24 hours twice weekly provide constant serum levels of estradiol 60 pg/mL (220 pmol/L) and estrone 50 pg/mL (185 pmol/L), which usually reduce menopausal symptoms and prevent osteoporosis. Occasionally, higher doses (eg, 75 μg/24 hours, 100 μg/24 hours) may be needed to control symptoms.

**Synthetic estrogens:** These chemical derivatives of estradiol are 100 times more potent, on a per-weight basis, than nonsynthetic estrogens in stimulating the production of hepatic proteins.
Synthetic estrogens have not been routinely used postmenopausally.

Adverse Effects

Estrogens may cause nausea, mastalgia, headache, and mood changes. They may also cause or aggravate serious disorders.

Endometrial hyperplasia and cancer: Only unopposed estrogen use (ie, without the addition of a progestin) induces endometrial hyperplasia. Unopposed estrogen also increases the risk of endometrial cancer (adenocarcinoma) about fourfold, from 1/1000 to 4/1000 women per year, depending on the dose and duration (minimum, 1 to 2 years). Prescribing estrogen in a reduced dose in a cyclic fashion reduces but does not completely eliminate the increased risk of cancer. Thus, concomitant use of progestins is advised for a patient with an intact uterus.
Progestins can prevent and reverse endometrial hyperplasia; use for 7 days/month significantly reduces the incidence of hyperplasia, and use for 10 to 13 days/month offers even greater protection. Progestins also reduce the incidence of endometrial cancer to below that of women not using estrogen replacement therapy.

**Ovarian cancer:** Estrogen replacement therapy may increase the risk of endometrioid cancer of the ovary (which accounts for 10 to 20% of all ovarian cancers), although this effect has not been proved. The effect of progestin use on this risk is unknown.

**Breast cancer:** Estrogen use may theoretically increase the risk of breast cancer, because breast tumors can be estrogen sensitive, estrogens can induce breast tumors in rats, and women with prolonged endogenous estrogen exposure (eg, due to early menarche, late menopause, or nulliparity) are at increased risk of breast cancer. However, the association between estrogen replacement therapy
and breast cancer is unclear, except for a possible modest increase in risk with use for 10 years or more. Nonetheless, estrogen replacement therapy may not be appropriate for menopausal women at particularly high risk of breast cancer. Adding a progestin may also increase the risk of breast cancer. The mitotic activity of the breast increases during the luteal phase, when maximum progestin secretion occurs (peak endometrial mitosis occurs during the follicular phase, when progesterone secretion is minimal). Moreover, progestins induce mammary ductal growth in rats. Therefore, the use of progestins in women without an intact uterus is unnecessary and possibly detrimental.

One of the questions resulting from studies is whether or not women taking HRT are at greater risk for breast cancer than women taking estrogen alone. A recent Swedish study, which included many women who had invasive breast cancer, found the excess risk to be quite high—2.5 percent annually. The
excess risk in this group continued for at least ten years after the last time they used HRT. In the largest study done to-date, only ten percent of women took HRT. In this study, there were over 2,000 new cases of breast cancer. The relative risk with ERT was 1.2 percent, while the risk with HRT was 1.4 percent. Those risks increased by 0.03 percent per year for ERT alone, while increasing by 0.12 percent per year for HRT. This may be due, in part, to the fact that progesterone has been found to increase breast density, which is a risk factor for breast cancer.

Elizabeth Barrett-Connor, MD, Professor and Chief of the Division of Epidemiology, University of California, San Diego, explained that there have been nine studies comparing women who got breast cancer while taking estrogen and women who got breast cancer who were not taking estrogen. All nine studies showed that the women who
developed breast cancer while taking estrogen had a better survival rate than those who developed breast cancer while not taking estrogen. "This could mean one of two things, either that estrogen causes a slower-growing tumor with a better prognosis, or that women taking estrogen have [an] earlier diagnosis. It seems that both are possible," said Dr. Barrett-Connor.

"The data are beginning to suggest that HRT may be more of a risk factor for breast cancer than ERT alone. Clearly, more studies are needed to determine if this is in fact the case," Dr. Barrett-Connor commented.

Although ERT and HRT may increase the risk of breast cancer, "studies done to-date indicate that those risks are relatively small and that the cancer seems to have a very good prognosis, as long as women maintain active surveillance with mammograms and self-examination," said Dr. Barrett-Connor.
**Cholelithiasis:** During the first year of use, oral estrogen replacement therapy increases the risk of cholelithiasis by 20%. Cholelithiasis probably occurs because estrogens increase the hepatic excretion of LDL cholesterol and reduce the amount of chenodeoxycholic acid in bile.

**Thromboembolic disease:** Postmenopausal use of estrogen replacement therapy appears to increase the risk of deep vein thrombosis and pulmonary embolism by about 2.5-fold. Thus, oral estrogen replacement therapy should not be given to a patient with a history of thromboembolic disorders.

**Hypertension:** Oral estrogen replacement therapy may increase the hepatic production of renin substrate or may stimulate the production of an aberrant form. Estrogen replacement therapy does not usually induce or exacerbate hypertension and may actually lower blood pressure in some women. Moreover, estrogen replacement therapy is not associated with an increased risk of stroke. When
blood pressure is increased due to estrogen replacement therapy, it is usually reversible when therapy is discontinued.

**Impaired glucose tolerance:** Although oral contraceptives can impair carbohydrate metabolism, the doses of estrogen replacement therapy used to treat postmenopausal symptoms do not appear to do so. Postmenopausal women with diabetes who take estrogen replacement therapy show no change, lower glucose levels, or reduced insulin requirements. Indeed, estrogen replacement therapy appears to increase the binding of insulin to its receptor, and in animal models, estrogen replacement therapy improves experimentally induced hyperglycemia.

Diabetic Women On Hormone Replacement Therapy Have Better Glycemic And Lipid Profiles *(September 26, 2002)* Diabetic and nondiabetic women on HRT have lower total cholesterol levels. Diabetic women who use hormone replacement therapy (HRT) were more likely to have their blood
glucose under control, and have lower cholesterol levels than women who never used hormone therapy, a study by University at Buffalo epidemiologists has found.

Women's Health Express Report Hormone Replacement and Menopause: What are the Issues? Data Presented from The 22nd Annual Meeting of The American Society for Bone and Mineral Research, Re-printed with permission of C 2000 Millennium Medical Communications told that Estrogen Replacement Therapy (ERT)—estrogen alone—and Hormone Replacement Therapy (HRT)—estrogen plus progesterone—have been found to reduce or reverse most menopausal symptoms. However, the long-term use of ERT and HRT appears to be associated with increased risk for breast cancer. Furthermore, the protection these therapies might provide against the onset of cardiovascular disease, remain controversial. Several studies presented at the 22nd Annual American Society of
Bone and Mineral Research examined the clinical evidence.

Li C, Samsioe G, Borgfeldt C, Bendahl PO, Wilawan K, Aberg A. Department of Obstetrics and Gynecology, Lund University Hospital, Sweden (2003 Mar) evaluate low doses of oral continuous-combined formulations of 17 beta-estradiol (E(2)) and norethisterone acetate (NETA) on carbohydrate metabolism in healthy postmenopausal women. A total of 102 women completed 12 months of treatment. An oral glucose tolerance test (OGTT) was performed at baseline and at 3, 6, and 12 months. They found that Oral low-dose E(2) 1 mg/NETA 0.5 mg regimen did not impair carbohydrate metabolism, but seemed to improve insulin sensitivity in healthy postmenopausal women.

With hormone replacement therapy (HRT), most research has focussed on osteoporosis, heart disease, and recently on Alzheimer's disease. The main
concern with HRT has been the question of breast cancer. Research indicates that with short-term use (less than 5 years) there is no increased risk. Most studies show a slight increase in breast cancer after more than 5 years of estrogen therapy after age 50. According to the Canadian Society of Obstetricians and Gynecologists, this translates into the real estimates of 2, 6, and 12 additional cases of breast cancer per 1000 women after 5, 10, or 15 years of use respectively. This slightly increased risk virtually disappears within 5 years of stopping. It is not clear if the increase is related to the dose or type of estrogen used. More research is needed in this area. A recent study showed a small increased risk of breast cancer associated with cyclic Provera 10mgs. The risk with other progestins, lower dosages, or continuous progesterone needs investigation.

The Heart and Estrogen/Progesterone Replacement Study (HERS) reported in 1998.\(^{15}\)
HERS studied the effect of 4 years of Premarin and Provera in women with previous known heart disease (heart attack or angina). This study found similar rates of new heart attacks in the women treated with HRT as in the women on placebo (sugar pills). One difference was that slightly more heart attacks occurred in the HRT groups during the first year of the study. The group of women on HRT experienced more deep vein thromboses (blood clots) and gall bladder disease.

The **Women's Health Initiative (WHI)** is currently evaluating the effect in healthy women of long term HRT on heart disease, osteoporosis, Alzheimer's disease and breast cancer. 25,000 women are enrolled in this study and the first results will be available in 2005. Results for heart disease, breast cancer and Alzheimer's disease will be available in 2007. Preliminary results in the heart disease portion of this study are similar to the HERS results.