Risks and Benefits of Estrogen Therapy

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Introduction
Estrogens are in use in healthy women as a contraceptive, for the treatment of climacteric complaints and as a preventive measure for postmenopausal osteoporosis. The practice of estrogen prescription shows great differences between countries, but probably more between cultures. For example, in Japan only 1.9% of married women use a hormonal contraceptive, while in The Netherlands nearly 50% of premenopausal women are prescribed oral contraceptives. For postmenopausal use, the figures are changing. After a period of rapidly increasing prescription, especially in the developed countries, the use of estrogens has fallen back as a result of publications about high risks for cardiovascular complications and endometrial and breast cancer. But the generation of women who accepted the oral contraceptive pill 20 years ago will by now have reached the age of the climacteric and are likely to expect relief from any menopausal symptoms they experience. The beneficial effect on bone metabolism in the prevention of postmenopausal osteoporosis is also getting more and more attention. For these reasons it is quite conceivable that the number of women seeking hormonal replacement therapy in the climacteric and after the menopause will rise sharply in the very near future. In the following paper, some aspects will be discussed; the effects of estrogens on lipid metabolism and coronary heart disease, on the mitogenic effect and cancer, and on bone metabolism and osteoporosis. In life assurance medicine, the extensive and increasing use of estrogens must be interpreted against the causes of death in women. In most countries, women die as a result of accidents, cardiovascular diseases or malignant neoplasms. Will the use of estrogens influence the mortality rates of cardiovascular diseases or malignancies in a positive or negative direction?

Lipid metabolism and estrogens
In the gut, nutritional fat is transformed to micelles, aggregates of molecules with a diameter of 2 to 6 nm (Newsholme et al. 1983). The aggregates consist of monoaoylglycerol, lysophosphoglycerol, fatty acids, bile salts and cholesterol. Bile salts, which are not absorbed, dissociate from the micelles at the surface of the intestinal epithelium. The absorption of the other components of the micelles is facilitated by a fatty acid binding protein in cell cytosol. Intracellularly, the fatty components are recombined into chylomicrons that consist of triacylglycerol 85%, phospholipids 8%, cholesterol 2%, cholesterolesters 3% and apolipoprotein-B 2%. The chylomicrons are excreted by exocytosis into the lymphatic system. Lipids are essential substances for life. Fatty acids supply energy and are basic elements for the production of cell membranes, prostaglandins, thromboxanes and other compounds. Cholesterol is an essential component of cell membranes too, but it is also a precursor of bile salts, hormones (e.g. cortisol, testosterone, estrogens) and vitamin D.

The lipids in plasma are chylomicrons, VLDL, LDL and HDL (Assmann 1982). Although these lipids all consist of the same components they differ in the location of production, function, molecular weight, diameter and ratios between triacylglycerol, cholesterol, cholesterolesters, phospholipids and the type of apolipoprotein. Chylomicrons are secreted by the intestinal cells, and transport fatty acids to adipocytes, muscles, heart and lungs. VLDL is produced in the liver and is also engaged in fatty acids transport. LDL and HDL are formed essentially in the plasma as remnants of VLDL after removal of triacylglycerol and phospholipids. LDL transports cholesterol to most, if not all, tissues, where it is bound with its apolipoprotein-B molecule on specific LDL receptors in the cell membranes (Brown et al. 1981, 1982). LDL enters the cells by means of endocytosis. Intracellularly free cholesterol is produced, which can be used for incorporation in cell membranes and the production of hormones or bile acids. The number of LDL receptors in the cell membrane is regulated by the intracellular cholesterol concentration. HDL contains, among other substances, phospholipids in the bilayer-lamellar structure of the outer surface. The plasma enzyme lecithin-cholesterol acyltransferase transfers fatty acids from the phospholipid onto cholesterol to form cholesterolesters, which then move towards the interior of the bilayer-lamellar structure. Consequently, the HDL takes up new cholesterol.
molecules from the cell membranes of many tissues and the arterial walls for transportation to the liver for the synthesis of bile acids. Moreover, subfractions of HDL can competitively displace LDL at the receptors of peripheral cells. The HDL-cholesterol concentration in plasma is influenced by different factors, e.g. physical activity, body weight, cigarette smoking and hormones.

During one menstrual cycle, no significant changes in LDL- and HDL-cholesterol could be observed in the study of Demacker et al. (1982). Other authors report an increased VLDL-cholesterol concentration at midcycle and a decrease in LDL-cholesterol in the second half of the cycle (Mattson et al. 1984). During the luteal phase HDL-cholesterol concentration increases (Kim et al. 1979, Mattson et al. 1984). In both men and women, plasma HDL-cholesterol concentration has a strong negative correlation with testosterone concentration, while plasma estradiol is not associated with HDL-cholesterol level in either sex (Semmens et al. 1983). Fertile women have lower serum levels of VLDL- and LDL-cholesterol and higher concentrations of HDL-cholesterol than men. After the menopause, the serum levels of VLDL- and LDL-cholesterol increase whilst HDL-cholesterol shows only a small increase or no change (Carlsson et al. 1975, Abbott et al. 1983, Tyrroer 1984). The HDL-cholesterol concentration decreases with increasing body weight in women (Bradley et al. 1978). Estrogens cause, in both the pre- and postmenopause, an increase in serum triglyceride and cholesterol concentration (Wynn et al. 1969, Krauss et al. 1979, Hennekins et al. 1979). However, after adjustment for the effect of obesity, post-menopausal hormone users have significantly lower levels of plasma cholesterol than nonusers, whilst the plasma concentration of triglycerides remain higher (Barret-Conner et al. 1979). The rise in serum triglyceride is a result of an enhanced influx from the gut (Kekki et al. 1971). Women using different estrogen/progestogen preparations as contraceptives have higher levels of VLDL- and LDL-cholesterol than nonusers, but they remain below the concentrations for men. HDL-cholesterol has a tendency to rise in premenopausal estrogen/progestogen users (Abbott et al. 1983). Women using oral contraceptives containing a relative low dose of estrogen combined with a medium or high dose of progestogen have higher concentrations of LDL-cholesterol than women not using hormones. Women using oral contraceptives that are high in estrogen and low in progestogen had higher concentrations of HDL-cholesterol than nonusers (Wahl et al. 1983). After the menopause, women have higher levels of VLDL-, LDL- and HDL-cholesterol concentrations than men. Estrogen users have VLDL- and LDL-cholesterol levels in the same range as men, but the HDL-cholesterol increases further in comparison to men (Wallace et al. 1979, Abbott et al. 1983, Wahl et al. 1983). Conjugated estrogens in a dose of 0.625 mg/day had no effect, but the 1.25 mg dose resulted in a fall in LDL- and a rise in HDL-cholesterol in postmenopausal women (Chetkowski et al. 1986). Estrogens alone, administered postmenopausally, cause enhanced plasma concentrations of HDL-cholesterol (Bradley et al. 1978, Krauss et al. 1979, Wallace et al. 1979), but progestogens alone result in a decrease of HDL-cholesterol (Krauss et al. 1979). The effect of progestogens on plasma HDL-cholesterol depends on the type of compound that is used (Fahraens et al. 1983). In women using combinations of estrogens with progestogens the effect on LDL- and HDL-cholesterol depends on the balance between both substances (Bradley et al. 1978, Crona et al. 1986). Estradiol administered in postmenopausal women via a transdermal therapeutic system in doses of 25 to 200 μg/24 hours, causes no changes in plasma concentrations of LDL- and HDL-cholesterol (Chetkowski et al. 1986).

**Coronary heart disease and estrogens**

Approximately two-thirds of the total cholesterol in plasma is transported in LDL and total cholesterol concentration shows a positive correlation with LDL-cholesterol (Assmann 1982). With increasing serum total cholesterol concentrations, the risk of developing premature coronary heart diseases rises (Wright et al. 1970). In young men (7-24 years of age), who died after accidents, fatty streaks in the aortic wall were studied as early signs of atherogenesis. In those with vessel changes, serum concentrations of total cholesterol, VLDL- and LDL-cholesterol were higher and HDL-cholesterol was lower, when compared with those without atherogenic signs (Newmann et al. 1986). An inverse correlation has been observed between plasma LDL- and HDL-cholesterol concentrations in men and in women (Miller et al. 1975). Plasma HDL-cholesterol concentrations in patients with ischemic heart disease is lower than in healthy controls. VLDL- and LDL-cholesterol show no difference between the two groups. From the Framingham Study (Gordon et al. 1977) it was confirmed that persons with low HDL-cholesterol levels are at higher risk than persons with high levels. The coronary risk among men and women aged 49 to 82 years, was positively correlated with LDL-cholesterol in this study. The plasma levels of triglycerides have little or no contribution to the incidence of coronary heart disease.

The incidence of coronary heart disease in premenopausal women is low. Both women with natural or surgical menopause have an increase in coronary heart disease compared with premenopausal women of the same age groups (Gordon et al. 1978). This suggests a possible preventive effect of estrogens in premenopausal women. On the contrary, in a retrospective study in a small group of women under 45 years of age with a myocardial
infarction, the proportion of patients who had used oral contraceptives during the month before admission was significantly higher among the patients than among healthy controls (Mann et al. 1975). Mortality rates from myocardial infarction were calculated for women of 30-39 years of age as 1.9 per 100,000 for nonusers and 5.4 for women using oral contraceptives. For the age group of 40-44 years, the mortality rates were 11.7 in the nonusers and 54.7 in the estrogen users (Mann et al. 1975). The combined effect of the use of oral contraceptives with other risk factors, such as cigarette smoking, was found to be synergistic (Mann et al. 1975, Jick et al. 1978). In a large size study, Slone et al. (1981) evaluated the rate of myocardial infarction in relation to current as well as discontinued use of oral contraceptives. For current users, the rate-ratio estimate was 3.5; the overall rate-ratio estimate for discontinued use was 1.2. When the duration of use was considered, the evidence of a relation between myocardial infarction and past use emerged, in particular in the age category of 40 to 49 years without known predisposing conditions (such as hypertension or diabetes mellitus). For use that lasted less than 5 years, 5 to 9 years and 10 or more years, the rate-ratio estimates were 1.1, 1.5 and 3.0 respectively. The amount of progestogens in oral contraceptives contributes to the risk of cardiovascular reactions. A positive correlation was found between the dose of progestogens and deaths from stroke and ischemic heart disease by Meade et al. (1980). In this study women using a 30 µg estrogen preparation had significantly fewer reports of death and ischemic heart disease than those with 50 µg of estrogen. The increased risk of myocardial infarction in current users and with long-term oral contraceptive use in the past was apparent in premenopausal women but not in postmenopausal women.

In the Lipid Research Clinics Program Follow-up Study, the relative risk of death in women aged 40 to 69 years using estrogens, compared with nonusers, was 0.54 in gynecologically intact women, 0.34 in hysterectomized women and 0.12 in bilaterally oophorectomized women (Bush et al. 1983). The lower risk of mortality in estrogen users can be accounted for, at least partially, by increased levels of HDL-cholesterol levels. In a study, comparing postmenopausal women with and without the use of estrogen containing drugs, but all with a nonfatal acute myocardial infarction, no evidence was observed for an association between current regular use of estrogens and nonfatal acute myocardial infarction (Rosenberg et al. 1976). In another study, women dying from ischemic heart disease were compared with living and deceased controls. Compared with living controls, women using estrogens had a risk ratio for death from ischemic heart disease of 0.43. Comparison with deceased controls gave a similar relative risk (Ross et al. 1981). Recently two prospective studies were published. In the Framingham Study, the morbidity was investigated in 1,234 postmenopausal women in the 12th biennial examination. No benefit from estrogen on coronary heart disease could be observed (Wilson et al. 1985). The second study concerned 32,317 postmenopausal women who were initially free of coronary disease. As compared with the risk in women who had never used hormones postmenopausally, the relative risk of coronary disease in those who had ever used them, was 0.5 and the risk in current users was 0.3. These last data support the hypothesis that the postmenopausal use of estrogens reduces the risk of severe coronary heart disease (Stampfer et al. 1985).

Mitogenic effect of estrogens
Steroid hormones influence the rate of protein synthesis or the type of protein that is synthesized in the target tissue (O'Malley et al. 1974). The free steroid hormone must cross the cell membrane, probably by simple diffusion, to bind to a specific receptor in the cytosol of the cell. The receptor exhibits very high specificity for particular steroids. The receptors, so far identified, are proteins which consist of two different subunits, A and B, each of which probably binds one steroid molecule. It is likely that the confirmation of the subunits change upon binding the hormone and this may facilitate transport of the complex into the nucleus. It is suggested that the B subunit possesses specific binding sites for the acceptors on chromatin, which identifies the position on the genome for the effect of the hormone. The subunit A dissociates and attaches itself to the DNA which causes some change that allows access of RNA-polymerase to the DNA so that this gene is then transcribed (Newsholme et al. 1983). It has been demonstrated that estrogens can be considered to act on susceptible cells as a promoting agent that is able to stimulate the multiplication of initiated cells (Moogavkar et al. 1980). In addition, it has been reported that progestogens, in the presence of estradiol, decrease DNA synthesis and cell multiplication in human carcinoma breast cells (Vignon et al. 1983). Progestogens are able to antagonize the estrogenic effect and could have a protective effect against the estrogenic promoting action. In the human endometrium, there are changes in estrogen and progesterone receptors during the cycle. In postmenopausal women with endometrial cancer, the disease apparently produces an endometrium that at risk for estrogen, with too many estrogen receptors and not enough progesterone receptors (Baulieu 1986).

Growing cells are characterized by a sequence of events leading to duplication of their constituents. These events occur in a strict temporal order during the cell cycle. The four phases of the total cycle are the M-phase, the period when the cell divides, the G1-phase, the gap between the
M-phase and the S-phase, the DNA-synthetic period, which is followed by the G2-phase, the gap between the S- and M-phase (Howard et al. 1953). During G1, cells increase in volume and in protein content and during G2 the mitotic apparatus is readied for cell division. There is considerable variability in the transit times of individual cells through the cell cycle (Adams 1980). Normal animal cells have nutritional, physical and hormonal requirements for growth. Nutritional requirements include a need for amino acids as well as trace metals and lipids. Physical requirements are best typified by the need for anchorage to a solid surface. Hormonal requirements manifest themselves in the need for polypeptide growth factors contained in plasma (Bockus et al. 1983). During growth arrest, the cell accumulates at the position of G0, a side-line of the cell cycle between the M- and G1-phase. Normal cells can remain in this quiescent state for extended periods of time with no loss of viability, but malignant cells lose the capacity to enter this state of growth arrest. The events through the cell cycle are regulated by growth factors. Some of the better characterized growth factors are insulin-like growth factor I and II (IGF-I and -II), epidermal growth factor (EGF), nerve growth factor (NGF) and platelet derived growth factor (PDGF). PDGF plays a key-role in the regulation of fibroblast cells, e.g., in the development of atherosclerotic plaques (Brown et al. 1984). IGF-I is produced in the liver and some other tissues. It is a potent stimulator of proliferation and differentiation of many cell types (Canalis 1985). During the cell cycle growing cells require IGF-I from a period following the M-phase until a time prior to the onset of the S-phase (Pardee et al. 1981). The way IGF-I and other growth factors influence the events of the cell cycle are under investigation. Estrogens inhibit the production of IGF-I in the liver (Wiedeman et al. 1976, Duursma et al. 1984). Clinical and laboratory data indicate that IGF-I contributes to the coordination of the balanced growth response of all body tissues as animals progress from infancy towards adulthood and possibly also during the rest of life. Malignant transformation could result from impairment of the pathways at the cellular level.

Endometrial and breast cancer and estrogens

After the menopause, the serum concentrations of estradiol decreases from 30 to 500 pg/ml to about 13 pg/ml (Judd 1976). The precursor of estrogens is androstendion which falls in concentration after the natural menopause from 1500 pg/ml to 830 pg/ml and after oophorectomy to about 180 pg/ml. In postmenopausal women, 25% of serum androstendion is still produced by the ovaries, 75% originates from the adrenals. Fatty tissues convert androstendion into estrogens and a positive correlation has been observed between estrogen production and body weight (Schindler et al. 1972, MacDonald et al. 1978). Obese women also have more endometrial neoplasia than slender women (MacDonald et al. 1974) and a relation was observed between body weight, plasma estradiol concentrations and endometrial cancer (Judd et al. 1980).

In 1954, Jensen et al. mentioned a possible relationship between estrogen and the development of cancer of the corpus uteri. In cancer patients, the menopause commenced later and they had been more often treated with estrogens than the average women. Cutler et al. (1972) affirmed this suspicion of a carcinogenic role of exogenous estrogens in patients with endometrial carcinoma. The risk-rate estimate for endometrial cancer increased with the duration of exposure to estrogens, from 5.6 for 1 to 4.9 years exposure, to 13.9 for 7 or more years (Ziel et al. 1975). In a larger material, the risk for endometrial cancer was 4.5 times greater among women exposed to estrogen therapy than in nonusers (Smith et al. 1975). A large number of publications appeared after these studies. In different areas in the United States, the incidence rates of endometrial cancer rose sharply in the 1970's. The incidence among middle-aged women changed most, by 40 to 150%, depending on the area (Weiss et al. 1976). In an affluent retirement community the risk-ratio for estrogen use for endometrial carcinoma was 8.0 and a dose response effect could be demonstrated (Mack et al. 1976). All these well documented studies allow only one conclusion, the use of estrogens increases the risk for endometrial neoplasia. This relation between estrogen consumption and endometrial carcinoma was further demonstrated in a large group in Seattle. From 1975 to 1977, there was a sharp downward trend in the incidence of endometrial cancer that paralleled a substantial reduction in prescription for replacement estrogens (Jick et al. 1979). An objection against these mentioned investigations may be that they are all retrospective studies. Only two prospective studies are available. Nachtigall et al. (1979) undertook a ten-year double blind study in 84 pairs of randomly chosen postmenopausal women, matched for age and diagnosis. The treated women received high-dose estrogens, cyclically with progestosterone. Statistically no difference was obtained for endometrial cancer between estrogen users and nonusers. Gambrell et al. (1980) observed the highest incidence of endometrial cancer, 359.1:100,000, in women using estrogens alone. In untreated women, the annual incidence was 248.3:100,000 and the lowest incidence, 56.4:100,000, was found in estrogen/progestogen users. These prospective studies affirm the carcinogenic effect for endometrial cancer of estrogens alone. The combination of estrogens with progestogens seems to protect women, not only from the carcinogenic effect of exogenous estrogens, but also they have less chance of endometrial cancer than untreated postmenopausal women.
Breast glands possess receptors for estrogens. After the publications about the relation between the use of estrogens and endometrial carcinoma, attention was paid to a possible effect in breast cancer. One of the first studies demonstrated a redoubling of the relative risk for breast cancer in postmenopausal women treated with conjugated estrogens for 15 years (Hoover et al. 1976). After bilateral oophorectomy the risk increased with the years of estrogen use, reaching risks of two to three times for users of ten years or more (Brinton et al. 1981). In a study of Jick et al. (1980) the use of oral contraceptives in women 45 years of age or younger did not influence the rate of breast cancer. In premenopausal women over 45 years of age, estrogen users had a higher incidence of breast cancer. Later, no increased risk was observed in a number of investigations for breast cancer in estrogen users (Nachtigall et al. 1979, Gambrell et al. 1979, Kaufman et al. 1984). In a prospective study in postmenopausal women, the lowest incidence of breast cancer, 67.3:100,000, was observed in estrogen/progestogen treated women. The incidence of mammary malignancy in the estrogen users was 141.1:100,000 and in the untreated women 342.3:100,000 (Gambrell et al. 1983). As in endometrial carcinoma, the combination of estrogens with progestogen seems to protect women from breast cancer.

Bone metabolism and estrogens

Plasma calcium homeostasis is maintained within a narrow range and many vital processes require an optimal concentration of ionized calcium in body fluids. Parathyroid hormone and 1,25(OH)₂ vit D are the most important hormones in plasma calcium homeostasis. Bone can be used as a buffer to supply for a calcium demand or to accommodate for a calcium surplus, at least temporarily. It must be emphasized that calcium homeostasis has priority over the regulation of bone mass. With longstanding calcitropic hormone, parathyroid hormone will induce monocytic precursor cells to transform to osteoclasts and stimulate these cells to reabsorb bone tissue. The hormonal system regulating calcium homeostasis influences bone homeostasis indirectly. Other factors, including other hormones and physical activity, play an important role in the homeostasis of the amount of bone. In castrated animals and in girls with multiple pituitary hormone deficiencies, growth is promoted by estrogens. In high doses, estrogens inhibit growth (Ranke et al. 1984). They also inhibit bone loss in postmenopausal women (Duursma et al. 1986). Neither the bone loss that occurs in postmenopausal women nor the beneficial effect of estrogen replacement therapy in such women, is well understood. Since it has not been possible to demonstrate the existence of estrogen receptors in bone cells (Nutik et al. 1974, Van Paassen et al. 1978), the effect of estrogens on bone metabolism must necessarily be indirect. Heaney (1965) and Nordin (1971) suggest an increased sensitivity of bone cells to parathyroid hormone after the menopause. Stevenson et al. (1981) assign an essential function to calcitonin in the protection of bone in premenopausal- and estrogen treated postmenopausal women, while Raisz et al. (1983) emphasize the increased 1,25(OH)₂ vit D synthesis and calcium absorption observed following estrogen replacement therapy.

All these hypotheses start out from calcitropic hormones and little attention has been paid to growth factors. In a study directed on the effect of three weeks of estrogen substitution in healthy postmenopausal women, bone formation, estimated as serum alkaline phosphatase concentration, decreased by 17%. Bone resorption, reflected in the urinary excretion of hydroxyproline and calcium, fell with 50% and 40% respectively. Serum concentrations of parathyroid hormone, calcitonin and 1,25(OH)₂ vit D did not change. The serum concentrations of IGF-I decreased and growth hormone increased (Duursma et al. 1984). After the administration of estrogens, the following sequence of events is supposed: The IGF-I production in the liver is suppressed and as a result of the negative feed-back between IGF-I and plasma growth hormone concentration, the latter increases (Berelowitz et al. 1981). IGF-I is a potent stimulator of proliferation and differentiation of many types of cells (Canalis 1985) and the fall in IGF-I after estrogen substitution inhibits the osteoblasts and osteoclasts or their precursor cells. On the other hand, growth hormone directly stimulates the osteoblasts (Slootweg et al. 1985). The net effect of estrogen substitution is a positive change in the balance between bone resorption and bone formation (Duursma et al. 1986). This model, based on the balance between IGF-I and growth hormone, fits very well with observations in the literature. Dequeker et al. (1982) found lower levels of serum growth hormone concentrations in postmenopausal women with osteoporosis than in a control group or in a comparable group of women with osteoarthritis without osteoporosis. Bennett et al. (1984) measured in osteoporotic women higher serum concentrations for IGF-I than in a healthy group of the same age between 60 and 70 years. Much is still unknown about the effect of estrogens on bone metabolism; however the model of the balance between IGF-I and growth hormone is consistent with recently published data.

Postmenopausal osteoporosis and estrogens

Under physiological conditions, bone mass declines with age in adults. After the age of about 50 years, a downward break in the curve of bone volume in females is observed. Bone loss in women over 50 years of age is on average 1.4% per year and throughout life about 40%.
In the early postmenopausal phase, bone loss in the lumbar spine is 6.6% per year (Krohner et al. 1982). Comparing bone loss in men and women for femoral neck and intertrochanteric femur, the rate of decrease in bone mineral density in men is two-thirds of that in women and for the lumbar spine it is one-fourth (Riggs et al. 1981, 1982). This explains why the female/male ratio for hip fractures is 2:1 and for vertebral fractures 8:1. Hip fractures are a cause of an increased mortality and disablement. During the first year after a hip fracture 27.1% of the patients died, 21.7% needed a wheelchair and 20.6% needed other resources. Only 30.6% had a complete rehabilitation and were ambulatory (Miller 1978).

Substitution with estrogens alone or in combination with progestogens prevents postmenopausal bone loss (Lindsay et al. 1976, Christiansen et al. 1980). Oophorectomy before 45 years of age is associated with an increased prevalence of osteoporosis in three to six years after operation (Aitken et al. 1973), but can be prevented by estrogen substitution (Lindsay et al. 1980). Henneman et al. (1957) were one of the first authors who described the beneficial effect of estrogens on the fracture rate in osteoporosis. In postmenopausal osteoporotic patients treated for two to twenty years with estrogens, no further loss of height and no further progression signs of osteoporosis were observed on radiographs of the spine. In osteoporotic patients treated with anabolic steroids, the number of new vertebral fractures was with 40 fractures per 1000 patient years, the same as in untreated women. Estrogens in a dose of 0.625 mg decreased the number to 25 and in women receiving 1.25 mg only 3 new fractures were seen (Gordon et al. 1973). In a large study, the effect of estrogens could be compared with other therapeutics in osteoporosis. The vertebral fracture rate in untreated patients was 834 per 1000 person years, 419 in those given calcium with or without vitamin D, 304 in those given fluorid and calcium with or without vitamin D, 181 in those given estrogens and calcium with and without vitamin D and 53 in those given estrogens, fluorid and calcium with or without vitamin D (Riggs et al. 1982). In women between 50 and 74 years of age, who had used estrogens for six years or longer, the risk of a fracture of the hip or lower forearm was 50 to 60% of that in women who had no substitution (Weiss et al. 1980). When estrogen substitution is stopped, the same rate of bone loss is observed as after oophorectomy or spontaneous menopause (Horsman et al. 1979, Christiansen et al. 1981). All the studies mentioned, and many others, demonstrate the beneficial effect of estrogen substitution on bone in postmenopausal women. The question of how long should estrogens be given for prevention of bone loss is not yet answered. A second question of whether all postmenopausal women or only the fast losers of bone be advised to use estrogens, is still unanswered. Contradictory results of investigations make it difficult to answer these questions. In one study, fast losers and slow losers of bone had the same plasma concentrations for different estrogens and androstendion (Manolagos et al. 1979), but in another study, women with vertebral fractures had lower plasma levels of estrogens and androstendion than postmenopausal women of the same age without fractures (Crilly et al. 1978). Some authors describe in a retrospective study only a beneficial effect on bone loss in postmenopausal women when treatment was started within five years after the menopause (Hutchinson et al. 1979). Others observed only a preventive effect when estrogen substitution was given at least during six years (Weiss et al. 1980, Paganini-Hill et al. 1981). The effect of estrogens on bone metabolism is dose dependant. 15 μg of ethinylestradiol or 1 mg 17β-estradiol prevent bone loss and 25 μg of ethinylestradiol or 2 to 4 mg of 17β-estradiol cause an increase in bone mass (Horsman et al. 1983, Christiansen et al. 1982). Addition of progestogens to estrogens does not influence the positive effect of estrogens on bone (Christiansen et al. 1981).

**Summary and conclusions**

The decision of healthy women to use estrogens depends on the beneficial effects they desire and the unwanted side effects they have to be aware of. The consequences for life assurance medicine do not play any role in this decision. Medical advisors of life assurance companies must consider the risks for an individual woman and for the total number of women that uses estrogens. The advantages and disadvantages will be summarized for pre- and postmenopausal women separately (Table 1).

**Premenopausal women**. The goal for the use of estrogens, the contraceptive effect, is beyond discussion. The use of estrogens in premenopausal women cause an elevation of the plasma concentrations of triglycerides, total cholesterol, VLDL-cholesterol and LDL-cholesterol, while HDL-cholesterol shows only a tendency to rise. Oral contraceptives with a relative high amount of progestogens and a relative low dose of estrogens result in an increase in LDL-cholesterol and no change in HDL-cholesterol level. Women using a pill with a relative high amount of estrogens and a relative low dose of progestogens will get no change in serum LDL-cholesterol concentration and have higher concentrations of HDL-cholesterol. The rate-ratio estimate for myocardial infarction in premenopausal women is higher in estrogen users than in nonusers. Both current and past users have a higher incidence for myocardial infarction. Although more coronary heart disease is observed, we must realize that the incidence of coronary heart disease in this age group is low and the increasing factor is small. Allowance must also be made for the decline in coronary heart disease
as a result of other factors (Feinleib 1984). Besides, modern contraceptives contain lower amounts of hormones. Under the age of 45 years oral contraceptives do not influence the incidence of breast cancer. In premenopausal women older than 45 years of age, an increased risk for breast cancer has been observed. From the point of view of gynecologists, it can be concluded that the overall balance of estrogen use in premenopausal women might be a slight increase in mortality rate, but recent developments seem to contradict this conclusion. No measures are necessary for the acceptance of women using oral contraceptives.

Postmenopausal women. All studies demonstrate the beneficial effect of estrogens on bone metabolism. Postmenopausal bone loss is prevented and with high doses of estrogens even an increase in bone mass has been observed. In osteoporotic women estrogen substitution causes a decrease in the number of new fractures. Estrogens alone cause a rise in plasma concentrations of triglycerides and HDL-cholesterol and a decrease in total cholesterol, VLDL-cholesterol and LDL-cholesterol. Progestogens alone give a fall in plasma HDL-cholesterol concentration. The effect of the combination of estrogens with progestogens depends on the ratio between these substances. In most studies, the relative risk of mortality by coronary heart disease is lower in estrogen users than in nonusers. Endometrial carcinoma is seen more in women who use estrogens alone. The risk of endometrial carcinoma increases with duration of exposure. The combination of estrogens and progestogens seems to have a preventive effect on the incidence of endometrial cancer. The incidence of breast cancer is lower in women using estrogens than in nonusers. The lowest incidence is observed in those who were prescribed estrogens and progestogens. The addition of progestogens does not influence the effect of estrogens on bone metabolism. In conclusion, in postmenopausal women, the use of estrogens, combined with progestogens, causes no increase in the mortality rate of cardiovascular diseases or malignancies. From the point of view of gynecologists, it must be mentioned that these women will live longer than nonusers.

Table 1
Effect of estrogens as oral contraceptive or postmenopausal replacement therapy.

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<th>Premenopausal women:</th>
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<td>— oral contraceptive</td>
<td>— estrogen alone</td>
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<td>— estrogen dominated pill</td>
<td>— progestogen alone</td>
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<td>— progestogen dominated pill</td>
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<td>— fracture incidence</td>
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effective
LDL = and HDL ↑
LDL ↑ and HDL =
increases with duration of use
increases with dose of progestogen
no influence < 45 years of age
increases ≥ 45 years of age
LDL ↓ and HDL ↑
LDL ↑ and HDL ↓
decreases, mostly in current users
increases with dose of estrogen
decreases with estrogens + progestogens
decreases with estrogens alone
decreases more with estrogens + progestogens
prevented
decreases in vertebral fractures
decreases in hip and forearm fractures
References


